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Ethylene Bisdithiocarbamates Decision Document. Final Resolution of Rebuttable Presumption Against Registration

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This Position Document addresses the risks and benefits of pesticide products containing the subject active ingredient. The Agency has determined that the use of products containing the subject active ingredient may meet or exceed a risk criterion described in 40 CFR Part 154. Potential hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of the subject active ingredient, whether such risks cause unreasonable adverse effects on the environment.

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Ethylene Bisdithiocarbamates

Decision Document

Final Resolution of Rebuttable Presumption Against Registration

Office of Pesticides and Toxic Substances
Environmental Protection Agency

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EXECUTIVE SUMMARY

This Decision Document continues the registration of the ethylene bisdithiocarbamate (EBDC) fungicides based on a consideration of the risks and benefits of these chemicals. This document responds to the rebuttal comments and additional studies; estimates human exposure and risks; describes the benefits of the EBDC's; develops regulatory options; and specifies the regulatory actions necessary to assure safety to the public and users of these chemicals.

The EBDC's consist of six broad spectrum fungicides--nabam, maneb, zineb, metiram, mancozeb and diammonium EBDC. These chemicals are used to prevent crop damage by fungi and to protect harvested products from deterioration. They are also used as slimicides in industrial cooling towers, sugar mills and pulp and paper mills. Approximately 30 million pounds are applied each year agriculturally and industrially in the United States.

A notice of rebuttable presumption against registration (RPAR) of the EBDC's was issued along with Position Document 1 (PD 1) on August 10, 1977. The RPAR was based on the presumption that the EBDC's and a metabolite, ethylene thiourea (ETU), posed three kinds of risk to human health or the environment: oncogenicity, teratogenicity and acute toxicity to aquatic organisms. Subsequent to PD 1, the Agency received rebuttal comments and additional studies on these risks.

The three risk criteria cited in PD 1--acute toxicity, oncogenicity and teratogenicity--were not rebutted outright so that further evaluation was needed. Three additional areas of concern were identified in PD 1--thyroid toxicity, mutagenicity and skin sensitization. The first two were found to meet RPAR risk criteria, while skin sensitization was determined not to meet an RPAR criterion.

After evaluating these potential risks in-depth, taking into account uncertainties associated with the risk estimates, considering the significant benefits of the EBDC's and weighing various regulatory options, the Agency has reached the following conclusions.

1. The potential risk of acute toxicity to aquatic organisms resulting from use of mancozeb on commercially grown wild rice will be mitigated through present cultivating practices and the addition of a statement to the label warning users of a hazard to fish.

2. Potential risks of teratogenicity and thyroid toxicity to commercial and agricultural applicators will be adequately reduced by requiring protective clothing.

3. Potential dietary exposure to homeowners can be reduced by highlighting preharvest intervals on labels of non-commercial (home use) products.

4. The issues of whether EBDC's or ETU pose a potential risk of oncogenicity, mutagenicity, teratogenicity and thyroid effects to man are subject to many uncertainties. The laboratory data on oncogenicity and mutagenicity are not adequate to resolve key scientific issues such as the mechanism of action of EBDC's and ETU. Additional data on the EBDC's and ETU are needed for the Agency to determine their potential for mutagenicity, to properly quantitate oncogenic risk and to better assess human exposure. Some data will be required now (metabolism, dermal penetration and mutagenicity), while further data needs, with particular emphasis on chronic studies, dietary residues and exposure, will be identified during a reregistration review scheduled in the near future.

In summary, the Agency will end the RPAR review and return the EBDC's to the registration process on the condition that registrants comply with the label changes and data requirements specified in this document. Within the next 2 years the Agency will conduct a full reregistration review of the EBDC's and other major agricultural fungicides. At that time, the data generated as a result of this RPAR decision will be evaluated, the risks of EBDC's will be reestimated and compared to risks from alternative fungicides, tolerances will be reassessed to the extent possible and the need for additional data or regulatory action will be determined.

ETHYLENE BISDITHIOCARBAMATES (EBDC's) DECISION DOCUMENT

I. INTRODUCTION

A. General Background and Organization

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, requires the Environmental Protection Agency (EPA) to review the risks and benefits of the uses of pesticides suspected of causing adverse effects to human health or the environment. On August 10, 1977, EPA issued a Rebuttable Presumption Against Registration (RPAR) Notice of pesticide products containing the ethylene bisdithiocarbamates (EBDC's), which are widely used broadspectrum protective fungicides. Position Document 1 (PD 1), published together with the RPAR Notice, provided background and supporting data for the presumptions of risk cited in the RPAR Notice. Specifically at issue in the RPAR action are the following six EBDC's that have uses registered with the Agency: diammonium EBDC, mancozeb, maneb, metiram, nabam and zineb (Table I-1). The rebuttable presumption was based on evidence showing that the EBDC's pose risks as follows: acute toxicity to aquatic organisms, oncogenic effects in test animals, and chronic or delayed toxicity causing teratogenic effects in test animals. In addition, the RPAR Notice of August 10, 1977, cited three other possible adverse effects of the EBDC's for which insufficient evidence existed to initiate a rebuttable presumption: mutagenicity, thyroid effects, and skin sensitization.

Since the RPAR against EBDC's was issued, the Agency has reviewed rebuttal comments and data submissions and has conducted in-depth risk and benefit analyses. This decision document responds to the submissions received during the rebuttal period, summarizes the risks and benefits associated with the EBDC's, and sets forth a regulatory decision.

This decision document contains five parts. Part I is this introductory section. Part II addresses the rebuttal and data submissions received and presents an evaluation of the potential risks of the EBDC's. It includes descriptions of the relevant laboratory data on risks, exposure data, and the Agency's present risk assessment. Part III is a use-by-use analysis of the economic benefits of the EBDC's. Part IV presents a range of regulatory options. Finally, Part V specifies the Agency's conclusions and regulatory actions based upon consideration of the risks and benefits of EBDC use.

Table I-1. EBDC Nomenclature

Common Name	Label Chemical Name	Trade Name(s)	
1. None	Diammonium EBDC	Amobam®	
2. Mancozeb*	**	Dithane® Manzate®	M-45 200
3. Maneb	Manganese EBDC	Manzate® Dithane®	 M-22
4. Nabam	Disodium EBDC	Chem Bam® Dithane®	 D-14
5. Metiram*	***	Polyram®	
6. Zineb	Zinc EBDC	Parzate® Dithane®	 Z-78

* Recognized in Europe but not yet established in the United States. These names will be used in this document for convenience.

** Zinc ion and manganese ethylene bisdithiocarbamate 80%, a coordination product of manganese 16%, zinc 2%, ethylene bisdithiocarbamate 62%.

*** Mixture of 5.2 parts by weight (83.9%) of Ammoniates of [ethylenebis (dithiocarbamato)] zinc with 1 part by weight (16.1%) ethylenebis [dithiocarbamic acid], biomolecular and trimolecular cyclic anhydrosulfides and disulfides.

B. Legal Background

1. The Statute

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (7 U.S.C. 136 et seq.), regulates all pesticide products, and Section 3(a) of the Act requires all pesticide products to be registered by the Administrator before they may be sold or distributed. Before the Administrator may register a pesticide, however, she must determine that its uses will not result in "unreasonable adverse effects on the environment" [Section 3(c)(5)(D)], defined by Section 2(bb) of FIFRA as "any unreasonable adverse risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide." In other words, any registration decision must take into account both the risks and the benefits associated with uses of the pesticide.

Section 6(b) of FIFRA authorizes the Administrator to issue a notice of intent to cancel the registration of a pesticide or to change its classification if it appears that the pesticide or its labeling "does not comply with the provision of [FIFRA] or, when used in accordance with widespread and commonly recognized practice, generally causes unreasonable adverse effects on the environment." Thus, the Administrator must cancel the registration of a pesticide should she determine that it no longer satisfies the statutory standard for registration that requires, among other things, that the pesticide "perform its intended function without unreasonable adverse effects on the environment" [Section 3(c)(5)(C)]. She may also cancel the registration of a pesticide if its labeling does not comply with the misbranding provisions of FIFRA, which requires the labeling to contain language "adequate to protect health and the environment" [Section 2(q)(1)(G)].

2. The RPAR Process

To implement its authorized functions, the Agency has designed the Rebuttable Presumption Against Registration (RPAR) process that involves gathering data on the risks and benefits associated with the uses of suspect pesticides. The RPAR process is set forth in 40 CFR 162.11, which describes various risk criteria and provides that an RPAR shall arise if the Agency determines that any of these criteria have been met.

C. Chemical Background

1. Chemistry and Physical Characteristics

The chemistry of the EBDC's is complicated by their instability and their propensity to form polymers. Their

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solubilities in water and other solvents vary, as do their melting points.

The EBDC's are generally unstable in the presence of moisture and oxygen, as well as in biological systems (Engst, 1977). A common contaminant, degradation product, and metabolite of all EBDC's is ethylenethiourea (ETU), an odorless white crystalline solid that is soluble in water but insoluble in common organic solvents such as acetone, ether, chloroform, and benzene (Table I-2). Other degradation products include ethylenebisdiisothiocyanato sulfide (EBIS), ethylenethiuram disulfide (ETD) and ethylenethiuram monosulfide (ETM) (Table I-3). EBDC residues are known to convert readily to ETU during the commercial processing or home cooking of various foods--in particular during the cooking or canning of spinach, carrots, potatoes, tomatoes, snap beans, and apples (Engst 1977).

a. Residue Chemistry: Soil

The mobility of the EBDC's in soil varies considerably, depending on their individual water solubilities as well as on soil types. The EBDC's, in general, are more mobile in wet and in sandy soils than in dry soil and in soil rich in organic matter (peat or muck). According to a laboratory study in which soil thin-layer chromatography (TLC) plates were used, nabam is more mobile than maneb, which in turn is more mobile than zineb--zineb being almost immobile (Helling et al. 1974).

Because both zineb and metiram are relatively insoluble in water, metiram is thought to be, like zineb, relatively immobile in soil (Jensen 1978). The degradation product ETU is generally water soluble and mobile.

The half-life of the EBDC's in silt loam soil ranges from 4 to 13 weeks, whereas the half-life of of ETU in the same soil is about 3 weeks (Rhodes 1977; Lyman and Lacoste 1975).

b. Residue Chemistry: Water

The EBDC's decompose rather rapidly in water. Mancozeb has been observed to have a half-life of less than 1 day in sterile water before degrading to ETU (Lyman and Lacoste 1975). Photolysis is a major degradation pathway for ETU (Cruichshank and Jarrow 1973; Ross and Grosby 1973). ETU itself has been observed to degrade after 8 hours of exposure to ultra-violet light (Rhodes 1977). Photolysis is enhanced by the presence of photosensitizers such as chlorophyll (Ross and Grosby 1973). Runoff studies have shown that only about 1 percent of mancozeb originally applied remained in runoff water and sediment (Jensen 1978).

Table I-2. Chemical, Physical and Biological Properties of EBDC's

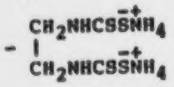
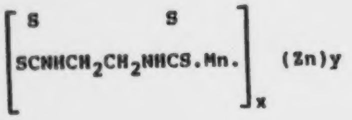
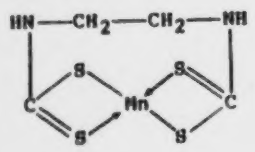
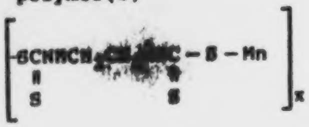
Chemical Structure	Molecular Formula	Molecular Weight	Physical Properties	Toxicity (LD_{50})	Solubility
Amobam®  $\mathrm{CH_2NHCS\overset{-+}{S}NH_4}$ $\mathrm{CH_2NHCS\overset{-+}{S}NH_4}$	$C_4H_{14}N_4S_4$	246.21	Unstable as dry material; aqueous solutions pale yellow to green; melting point 72.5° to 72.8°C (2).	---	Soluble in water; slightly soluble in alcohol and acetone; insoluble in ben- and heptane (2).
Mancozeb  $\left[\mathrm{\overset{S}{S}CNHCH_2CH_2NH\overset{S}{C}S.Mn.}\right]_x \mathrm{(Zn)y}$	Variable (see Table 1)	Indefinite	Greyish-yellow powder which decomposes before melting; flash point138°C (3).	>8,000 mg/kg	Practically insoluble in water and in most organic solvents (3).
Maneb a. Monomer 	$C_4H_6N_2S_4Mn$	265.3	Yellow crystalline solid which decomposes before melting and on exposure to moisture or to acids (3).	6,750 mg/kg	Slightly soluble in water and insoluble in most organic solvents (3).
b. polymer(s) 	$(C_4H_6MnN_2S_4)x$	Indefinite	Light-colored solid which decomposes before melting and on exposure to moisture or acids (3).	---	Similar to monomer

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Table I-2. Chemical, Physical and Biological Properties of EBDC's (continued)

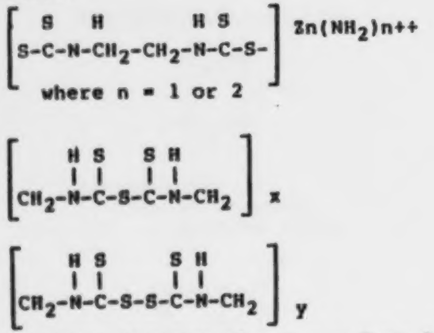
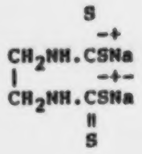
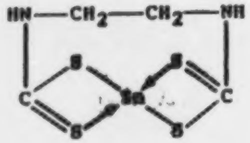
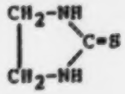
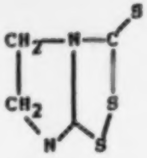
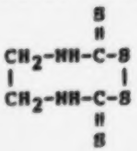
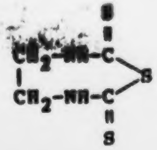
Chemical Structure	Molecular Formula	Molecular Weight	Physical Properties	Toxicity (LD_{50})	Solubility
Metiram  $\left[\mathrm{S{-}\overset{S}{C}{-}\overset{H}{N}{-}CH_2{-}CH_2{-}\overset{H}{N}{-}\overset{S}{C}{-}S{-}}\right]\mathrm{Zn(NH_2)n^{++}}$ where n = 1 or 2 $\left[\mathrm{CH_2{-}\overset{H}{N}{-}\overset{S}{C}{-}S{-}\overset{S}{C}{-}\overset{H}{N}{-}CH_2}\right]_x$ $\left[\mathrm{CH_2{-}\overset{H}{N}{-}\overset{S}{C}{-}S{-}S{-}\overset{S}{C}{-}\overset{H}{N}{-}CH_2}\right]_y$ where the sum of x + y = 2 or 3	Variable (see Table 1)	Indefinite	Light yellow solid which melts above 120°C with decomposition; unstable under strongly acid or alkaline conditions or a combination of heat and moisture (4).	>10,000 mg/kg	Practically insoluble in water and in most organic solvents; soluble with decomposition in pyridine (Martin 1974).
Nabam  $\begin{array}{l}\mathrm{CH_2NH.\overset{S}{C}SNa} \\ \mid \\ \mathrm{CH_2NH.\underset{S}{C}SNa}\end{array}$	$C_4H_6N_2Na_2S_4$	256	Colorless crystals of limited stability; generally marketed in solution (3).	395 mg/kg	Soluble in water (20%) to form yellow solution (3).
Zineb a. Monomer 	$C_4H_6N_2S_4Zn$	275.8	Off-white solid which decomposes before melting; negligible vapor pressure at 25°C; somewhat unstable to light, heat and moisture (3,6).	>5,200 mg/kg	Practically insoluble in water (10 ppm at 25°C) but soluble in pyridine, chloroform, and carbon disulfide (3,5).
b. Polymer(s) $\left[\mathrm{S.CS.NH.CH_2CH_2NH.CS.S.Zn}\right]_x$	$(C_4H_6N_2S_4Zn)_x$	Indefinite	Light-colored powder produced when precipitated from concentrated aqueous solutions of Amobam® or nabam with zinc sulfate (3,7).	---	Similar to monomer

Table I-3. Known EBDC Degradation Products

Name and Chemical Structure	Molecular Formula	Molecular Weight	CAS Name	CAS #	Physical/Chemical Properties
Ethylenethiourea (ETU) 	$C_3H_6N_2S$	102.2	2-Imidazolidinethione	96-45-7	White crystals melting at 203° to 204°C; soluble in water; insoluble in acetone, ether, chloroform, and benzene (11).
Ethylenebisdiisothiocyanato sulfide (EBIS) 	$C_4H_4N_2S_3$	176.3	3H-Imidazo [2,1-c]-1,2,4-dithiazole-3-thione,5,6-dihydro	33813-20-6	White powder that melts at 121° to 124°C.
Ethylenethiuram disulfide (ETD) 	$C_4H_6N_2S_4$	210.3	1,2,4,7-Dithia-diazocine-3,8-dithione, tetrahydro-	3082-38-0	
Ethylenethiuram monosulfide (ETM) 	$C_4H_6N_2S_3$	178.3		33813-20-6*	

*Chemical Abstracts Service assigns the same registry number to ETM and EBIS because the chemical structure for what had been referred to as ETM was shown in 1971 to be actually that of EBIS.

c. Residue Chemistry: Plants

ETU is one of several metabolites found when EBDC's are applied to plants. On plants, nabaim is transformed to ETU, ETM, ethyleneurea, 2-imidazoline, diisothiocyanate and other metabolites (Sijpesteijn and Vonk 1975).

Unlike the parent EBDC's, ETU is taken up by the plant root systems, translocated, and metabolized (Engst 1977). Studies in which the roots of corn, lettuce, tomato, and pepper seedlings were treated with ETU have shown that ETU is rapidly absorbed by roots and subsequently translocated to the foliar tissues. ETU was then degraded very rapidly; essentially none was detected after 20 days (Hoagland and Frear 1976). When cucumber seedlings were exposed to aqueous solutions of nabam or suspensions of zineb or maneb, ETU was rapidly absorbed by roots and translocated to the plants. ETU appeared to be stable for at least 2 weeks in seedlings treated 2 days via the roots (Vonk and Sijpesteijn 1970 and 1971).

d. Residue Chemistry: Animals

Evidence suggests that the EBDC's are rapidly metabolized in cows, though not so rapidly or thoroughly that no residues are detectable. Milk from a single cow that was fed ^{14}C-mancozeb contained about 1.5 percent of the radioactive material originally ingested (Lyman 1971). However, milk from three cows that were fed ^{14}C-ETU contained about 31 percent of the radioactive material originally ingested (Lyman 1971).

e. Metabolism and Pharmacology

Animal metabolism of the EBDC's is rapid and ETU and EBIS are major metabolites. Carbon disulfide and dimethylamine are formed in rats treated orally with mancozeb, maneb and zineb (Lyman 1971; Seidler et al. 1970; Vonk 1974; Truhaut 1973). Formation of these metabolites is expected following oral ingestion of EBDC's due to the acid environment of the stomach. Truhaut et al. (1973) identified EBIS, ETU, EU (ethyleneurea) and EDA (ethylenediamine) in the feces and urine of rats treated with mancozeb. After a single oral dose of ^{14}C mancozeb in rats, about 15 percent of the total radioactivity was found in the urine and about 71 percent (47 percent as unchanged mancozeb) appeared in the feces (Lyman 1971). Before elimination, radioactivity localized in the thyroid gland. Measurements indicated that roughly 18 percent of EBDC's was converted to ETU. Within 5 days after a single oral dose of radiolabeled maneb was administered to rats, about 55 percent of the total radioactivity was found in the urine and feces (Seidler et al. 1970). Metabolites identified were EDA, ETU and EBIS. ETU and EBIS were the major metabolites found in urine of rats treated with zineb (Truhaut 1973).

hepatic mixed-function oxidase activity. Moriya et al. (1979) showed that maneb, disulfiram and carbon disulfide inhibited the mutagenicity of 1,2-dimethylhydrazine and azoxymethane in the host-mediated assay, presumably by inhibiting their in vivo metabolism. Van Bladeren et al. (1981) showed that co-administration of disulfiram and 1,2-dibromoethane led to enhanced conversion of the latter to S-2-bromo ethyl glutathione, which is highly mutagenic. The enhancement of this metabolic pathway was caused by inhibition by the disulfiram of the cytochrome P-450 mediated oxidation of dibromoethane to mercapturic acid.

In 1978, Yoshida and Neal investigated the inhibition of hepatic cytochrome P-450 concentrations and monooxygenase activity (benzphetamine metabolism) by EBIS, one of the major metabolites of the EBDC's. They found that EBIS inhibits hepatic ALA synthetase activity in mice within two hours following its administration. Because ALA synthetase is a rate-limiting enzyme in heme synthesis, the authors postulated that inhibition of this enzyme, followed by a decreased availability of heme for the synthesis of cytochrome P-450, is consistent with the decreased oxygenase activity observed 12-24 hours after administration of EBIS.

Miladi et al. (1981) studied the effects of nabam and zineb on hepatic cytochrome P-450 enzymes. After 24 hours, a single oral dose of nabam or zineb causes a reduction in the biotransformation of animopyrene and of aniline in the hepatic microsomes of the rat. The effect of nabam is more pronounced than that of zineb. Both fungicides reduce the level of cytochrome P-450 and induce the formation of the inactive form, cytochrome P-420. No binding of the dithiocarbamates to the cysteine residues of the hemeprotein was established.

The two fungicides had a greater effect on the metabolism of type II (substrate) molecules - such as aniline - than on the metabolism of type I molecules such as aminopyrene. Both of these enzyme activities are dependent on cytochrome P-450. The Zn^{++} ion, when administered alone, had no effect on these enzyme activities or on the concentration of cytochrome P-450. Nabam had a greater effect than did zineb on the concentration of cytochrome P-450 and on the metabolism of both aniline and aminopyrene. This may be because of its greater absorption through the gut. For both fungicides, reduction of P-450 was accompanied by occurrence of P-420, its denatured form, and no bonding of the fungicides to SH groups of cysteine in the enzyme was found. Zemaitis and Greene (1979) showed that a variety of thiuram disulfides and dithiocarbamates impaired microsomal aniline hydroxylase and carboxylesterase activities. Of these, the reduced thiols, dimethyl-dithiocarbamate and diethyldithiocarbamate also caused significant decreases in cytochrome P-450 activity as well as ethylmorphine activity.

These results suggest that the decrease in level of cytochrome P-450 and the inhibition of hepatic mixed function oxygenase activity is a result of interaction of these thiono sulfur compounds or their metabolites with the macromolecules of the endoplasmic reticulum. A variety of mechanisms appear to be involved.

2. Registered Uses and Production

At least 27 million pounds (active ingredient) of the EBDC's are used annually in the United States [USDA/State/EPA EBDC Assessment Team (USDA/EPA 1978)]. The EBDC's are registered for use as fungicides on fruits, vegetables, small grains, nuts, tobacco seed beds, field crops, floral and ornamental plants, pine nurseries (including Christmas trees), turf grass, and grass grown for seed. They are used also as slimicides in water cooling systems, sugar mills, and pulp and paper mills.

3. Tolerances

The United States established the first tolerances for pesticides under Section 408 of the Federal Food, Drug and Cosmetic Act in 1955 after public hearings conducted by the Food and Drug Administration (FDA). Zineb was the only EBDC fungicide for which tolerances were set at that time. Tolerances of 7 parts per million (ppm) of zineb on "fruits and vegetables" were established on "very little data showing residues from actual commercial use" and with the knowledge that oral administration of zineb to male and female weanling rats at 5 and 2,000 ppm for 10 days produced thyroid hyperplasia at the high dosage but not at the low one. Studies published in 1948 had reported definite goitrogenic effects associated with oral administration of 1,000 ppm of another EBDC, nabam, to weanling rats for 9 to 10 days (Seifter et al. 1948). The two companies holding patents on zineb at the time, Rohm and Haas Company and E. I. Du Pont de Nemours and Company, had requested tolerances of 20 ppm on various fresh fruits and vegetables.

Maneb tolerances were first established in October 1955 at the request of Du Pont [Pesticide Petition (PP) 21]. A 7 ppm tolerance was allowed for maneb on more than 20 crops.

In 1957, tolerances for zineb on spinach, lettuce, and six other related crops were increased from 7 ppm to 25 ppm. New tolerances of 25 ppm on Chinese cabbage and romaine were granted with the condition that the interval between application and harvest be increased since, as noted by the chemistry reviewer, "contradictory to our previous information indicating chemical instability and rapid dissipation of dithiocarbamate residues, the Rohm and Haas residue data show that residues of the dithiocarbamates are quite persistent" (Ramsey 1957). Data supporting these two petitions

(PP 76 and 101) were obtained from a 2-year feeding study in rats and a 1-year feeding study in dogs (Smith et al. 1953).

The first mancozeb tolerance was established in December 1962 for 15 ppm on bananas (PP 374). The first metiram tolerances were established in July 1967 for five crops (apples, celery, cantaloupe, cucumbers, and tomatoes [PP 488]). The highest metiram tolerance was 7 ppm on apples. Toxicity data submitted in support of these tolerances included 2-year feeding studies of dogs and rats and a 3-generation rat reproduction study.

Final action on a tolerance petition for 1 ppm of zineb on potatoes, submitted in 1970, was never taken because of notification by FDA (Wodicka 1971) that results of a FDA study of rats fed ETU were confirming findings of carcinogenic activity reported previously (Innes et al. 1969). These results, plus the fact that EPA chemists had found ETU in commercial EBDC formulations and at enhanced concentrations with elevated temperature and humidity (Davis 1971), led those in charge of setting tolerances to recommend in October 1971 revocation of EBDC tolerances for all uses except those for which no residues were detected (McFarland 1971; Williams 1971; Cummings 1971). No action was taken on revocation, primarily because evidence that there were significant residues of ETU on crops was insufficient. Representatives of three principal EBDC producers (Du Pont, Rohm and Haas, and FMC) met with EPA in early 1972 and agreed to work with the Agency to reduce the tolerances for the major crops on which the EBDC's are used (Farkas 1972).

Subsequently, tolerances for EBDC residues on major crops were lowered. Over 150 tolerances are currently established for the EBDC's. Tolerances for EBDC residues in or on raw agricultural commodities are listed in 40 CFR (Code of Federal Regulations) 180.176 (mancozeb), 180.110 (maneb), 180.115 (zineb), and 180.217 (metiram). Interim tolerances for mancozeb, metiram, and zineb are listed in 40 CFR 180.319. Tolerances for mancozeb as a food additive in raisins, cereal grain flowers, and bran are given in 21 CFR 193.460 and as a fungicide in animal feeds milled from barley, oats, rye, and wheat in 21 CFR 561.410.

Uses of nabam as a slimicide in sugar mills and in the manufacture of paper and paperboard that contact food are permitted by the FDA, Department of Health and Human Services, under the conditions specified in 21 CFR 173.320, and 21 CFR 176.300 respectively.

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II. ANALYSIS OF REBUTTALS AND ASSESSMENT OF RISKS

A. Analysis of Rebuttals

As stated in 40 CFR 162.11, respondents may rebut any presumption against a pesticide by showing either that the Agency's initial determination of risk was in error or that exposure to the pesticide is not likely to result in any significant chronic adverse effects. The rebuttable presumption against registration of pesticide products containing the EBDC's drew responses concerning the three presumptions: acute toxicity of aquatic organisms, oncogenic effects and teratogenic effects. Comments were also received concerning the possible adverse effects of thyroid aberrations, mutagenic effects, and skin sensitization. All submissions received during the rebuttal period, together with the Agency's responses, are reviewed below.

1. Acute Toxicity to Aquatic Organisms

The Agency received responses from three registrants: E.I. Du Pont de Nemours and Company (30000/18:33E), Rohm and Haas Company (30000/18:132B), and FMC Corporation (30000/18:10B). The original presumption was based on Agency calculations that maneb and zineb applied to cranberries, according to label directions, result in concentrations (4.4 ppm and 3.52 ppm, respectively) greater than one-half the acute LC_{50} for two representative species, bluegills and *Daphnia magna*. In addition to the rebuttal submissions received in connection with this presumption, additional data (McCann 1977) concerning EBDC (mancozeb) used on wild rice fields have become available. The available data indicate that for cranberry field applications the presumption has been rebutted and for wild rice field applications the risk criterion for acute toxicity to aquatic organisms [40 CFR 162.11(a)(5)(3)(i)(B)(3)] has been exceeded.

a. Rebuttal Pertaining to Exposure: Cranberry Fields

In rebuttal, E.I. Du Pont de Nemours and Company (30000/18:33E) claimed that, "Applications of the fungicides, when applied as directed on the registered labels and as is the agricultural practice, are not made at, or near to, a time when the cranberry fields are covered with water." Similar arguments were submitted by Rohm and Haas Company (30000/18:132B) and FMC Corporation (30000/18:10B). These rebuttals were supported by written statements or by interviews from persons knowledgeable about the techniques of cranberry farming: Dr. Erving Demoranbill of Massachusetts (30000/18:33E), Dr. Phillip Marucci of New Jersey (30000/18:116), Dr. Ronald Boone of Wisconsin (30000/18:381), and Dr. Peter Bristow of Washington (30000/18:33E). The respondents pointed out further that no fish kills traceable to maneb or zineb have been reported.

Agency Finding:

The rebuttals are accepted. All interviews concerning cranberry field application practices were verified by the Agency. In addition, the EPA Pesticide Episode Reporting System (PERS) indicated no recorded instances of fish kills associated with the use of maneb or zineb under actual field conditions (Hogan 1978). The three incidents of fish kills associated with the EBDC's that are known to the Agency through other sources involved either misuse, accident, or a second active ingredient more acutely hazardous to fish than the EBDC's (Markley 1978).

b. Additional Agency Findings Pertaining to Risk: Wild Rice Fields

Since the RPAR against the EBDC's was issued, data have become available that indicate that use of mancozeb on wild rice fields in Minnesota poses an acute toxic risk to aquatic organisms. In an EPA laboratory study (McCann 1977), a 96-hour LC_{50} of 0.64 ppm mancozeb was measured for rainbow trout. Application of mancozeb, an EBDC product that is labeled for use against wild rice blight in Minnesota at the maximum rate of 1.6 pound/acre, could result in a 1.17 ppm concentration of mancozeb in a 6-inch layer of water.

Agency Finding:

Because this concentration is more than one-half the acute LC_{50} for rainbow trout, use of mancozeb on wild rice fields exceeds the risk criterion for acute toxicity to aquatic organisms.

c. Comments Submitted on Exposure: Wild Rice Fields

Although use of mancozeb in wild rice fields was not presumed against in PD 1, Rohm and Haas Company (the registrant of the mancozeb product used in Minnesota wild rice fields) submitted (1) a letter testifying to the absence of deleterious effects in organisms taken from mancozeb-treated paddies [30000/18:132S (Confidential)] and (2) residue analyses for mancozeb on wild rice and environmental samples (paddy soil and ditch water) [30000/18:132N (Confidential)]. The letter, from Dr. James A. Percich of the University of Minnesota, addressed, in very general terms, the safety of mancozeb when used according to "normal commercial practice."

Agency Finding:

The Agency concluded that the evidence presented does not negate the possibility that use of mancozeb on wild rice fields poses a risk of acute toxicity to aquatic organisms. The letter from Dr. Percich referenced no data, either

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qualitative or quantitative, such as population sizes of wildlife species before treatment, estimated numbers of organisms observed, correlation of observation dates with pesticide application, or related residue values in water, sediments, plants, and local fauna.

Concerning the residue analyses, no information was provided on the species of minnows sampled, the number of fish sampled, their size, or collection dates. Nor was a rationale provided for the long interval (16 to 18 days) between the last application of EBDC and collection of samples for residue analysis. Data on samples collected from 1 to 3 days after application would have been more pertinent to the issues of risk.

The Agency has further evaluated the potential for acute toxicity to aquatic organisms in Section II.C.

2. Oncogenicity

The Agency received submissions from five respondents: E.I. Du Pont de Nemours and Company (30000/18:33E), Rohm and Haas Company (30000/18:132D), FMC Corporation (30000/18:10B), Montedison Company (30000/18:145A), and the Environmental Defense Fund (30000/18:382).

The original presumption was based on five studies that reported positive oncogenic responses when either maneb, zineb, or ETU was tested on laboratory animals (mice or rats) (42 FR 40618). These studies were summarized by the EDA's Carcinogen Assessment Group (Albert, 1979) as follows. Balin (1970) observed increased lung adenomas in mice fed weekly doses of maneb (500 mg/kg body weight) by stomach tube for 6 weeks. Likewise, Chernov et al. (1969) observed increased lung adenomas in mice fed weekly doses of zineb (3500 mg/kg body weight) by stomach tube for 6 weeks. When weekly doses of zineb were reduced to 1750 mg/kg body weight but continued for 11 weeks, lung adenomas were again observed in treated animals but not in controls. Innes et al. (1969) observed marked increases mainly in liver tumors, and also in lung tumors and lymphomas in mice fed single daily doses of ETU (646 ppm) for over 80 weeks. Ulland et al. (1972) fed two different doses of ETU (350 and 175 ppm) daily to rats for 18 months. Thyroid carcinomas developed in test animals at both dose levels but did not develop in controls. Graham et al. (1975) fed ETU to rats at doses of 500, 250, 125, 25, and 5 ppm for nearly 2 years. Dose-related thyroid carcinomas were produced at 500 and 250 ppm; thyroid adenomas at 500, 250, and 125 ppm; and thyroid hyperplasia mainly at 125, 25, and 5 ppm.

The material submitted during the rebuttal period does not invalidate the studies on which the presumption of oncogenicity was based, nor is the presumption rebutted. (Table II-1 presents a summary of the available oncogenicity studies.) However, the studies involving maneb and zineb (Balin 1970; Chernov et al. 1969) do not constitute a sufficient basis on which to quantitatively assess oncogenic risk. Because good evidence exists that EBDC metabolizes into and is contaminated by ETU, the Agency's cancer risk assessment has focused on exposure to ETU (Section II.D)

a. Rebuttals Pertaining to RPAR Studies

(1) Rebuttals Pertaining to Balin (1970) and Chernov et al. (1969)

Several respondents raised parallel objections concerning the Balin (1970 and Chernov et al. (1969) studies, contending:

- Inadequate detail was reported and, therefore, the scientific validity of the studies is questionable.

Du Pont (30000/18:33E), Rohm and Haas (30000/18 132B) and Montedison (30000/18:145A) contended that Balin (1970) inadequately characterized test material, the nature of controls, the growth performance and sex of test animals, and the details of histopathology. Du Pont (30000/18:33E) enumerated failings analogous to those cited above in connection with Balin, additionally contending that the initial number of animals in the test groups was unspecified. FMC (30000/18:10B) argued further that Chernov et al. presented no evidence demonstrating that the adenomas in the controls were like those in the treated groups, and there were no data showing a correlation between tumor incidence and amount or duration of exposure.

- The maximum tolerated doses in both studies were much higher than the "near maximum tolerated doses" of maneb and zineb used in the Innes et al. (1969) mouse study, in which no pulmonary adenomas were observed.

Du Pont (30000/18:33E), Rohm and Haas (30000/18:132D), and Montedison (30000/18:145A) questioned the maneb dosage used by Balin (500 mg/kg) on the basis that the animal mortality was very high (75 percent). The zineb dosages used by Chernov et al. (1750 and 3500 mg/kg as compared to 464 mg/kg body weight used by Innes et al.) were, likewise, questioned. FMC (30000/18:10B) in particular challenged the validity of Chernov et al., contending that metabolism of a very high dose once a week might differ from metabolism of a smaller dose ingested daily and, furthermore, that the intubation technique used might have caused aspiration or intratracheal administration (lunging) of the zineb.

Table II-1. Summary of Oncogenicity Studies for ETU and EBDC's

Compound	Author	Test	Result
ETU	*Innes (1969)	85-week mice feeding, 2 strains	Positive for liver adenomas, p = <0.001[a]
	Innes (1969)	78-week, single subcutaneous injection. Two strains, mice	Negative
	*Bionetics, Res. Lab. (Ulland, 1972)	18-month rat feeding	Positive for thyroid carcinomas p = <0.001[b]
	*FDA (Graham, 1975)	2 - 24-month rat feeding	Positive for thyroid carcinomas, adenomas and hyperplasia p = <0.001[c]
	Gak (1976)	24-month, rat and hamster feeding	Positive for rats; negative for hamsters
MANEB	*Balin (1970)	9-month, mice, by gavage	Positive for lung adenomas p = 0.05[d], p = 0.007[e]
	Innes (1969)	78-week, single subcutaneous injection, mice	Negative
		80-week, oral feeding, mice	Negative
	Clayton (1959)	2 year, oral, rat	Inadequate, but negative
ZINEB	*Chernov, Khitsenko (1969)	Oral dosing, two strains mice, short term	Positive for lung adenomas p = 0.01[f]
	Blackwell-Smith (1953)	Long-term, rat	Inadequate, but negative
	Innes (1969)	78-week, single subcutaneous injection, mice	Negative

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[a] Both strains, both sexes
[b] Both sexes, high dose
[c] Carcinomas in both sexes at two highest doses
[d] C57BL at 9 months
[e] A at 9 months
[f] C57BL

*Studies on which original rebuttable presumption was based.

- Mice are inappropriate test animals by which to judge the oncogenicity of a chemical in man.

Both Du Pont (30000/18:33E) and Rohm and Haas (30000/18:132D) argued that many toxicologists consider mice to be a poor model on which to judge the oncogenicity of a chemical in man. Du Pont (30000/18:33E) submitted the agreement of the 1973 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues that "there is a serious lack of knowledge regarding the processes involved in the development of liver tumors by mice and that it would be unwise to classify a substance as a carcinogen solely on the basis of evidence of an increased incidence of tumors of a kind that may occur spontaneously with such a high frequency" (WHO 1974).

Agency Finding:

The Agency disagrees with the first two arguments. The studies conducted by Balin and Chernov et al. were deficient in design, execution, and evaluation; survival was poor; and histopathological analysis was limited (Albert 1978). However, available data are adequate to establish that the number of tumors in the experimental group of the A strain mice in the Balin study was significantly greater (p = .007) than that in the controls and that the incidence of lung adenomas in strain C_{57}BL mice fed zineb by Chernov et al. was significantly greater than that in the controls. The Agency maintains further that these positive test results are not invalidated by the strength of the dosages used, nor does a poor survival rate (Balin) negate the significance of observed oncogenic responses. It is acknowledged that the dosage used by Balin may have killed the animals before tumors could develop. However, the fact remains that tumors significantly greater than those observed in controls did develop in the mice that survived.

With regard to the respondents' objection to mice as test animals by which to assess carcinogenic potential, the Agency reaffirms its position that mice are acceptable models from which to predict cancer risk and that positive oncogenic responses in mice constitute indications of human carcinogenicity, especially when coupled with positive responses on other organs and other species. A comparison of results from studies in rats and mice with known human carcinogens has shown a high correlation between results in both rats and mice and results in humans (Albert 1979a). However, the weight given to a particular study will of course depend on its design and conduct, on the nature of the response, and on many other factors (Anderson 1978). Because of the deficiencies of these studies, the Agency has concluded that the data from these studies do not constitute sufficient evidence upon which to quantitatively assess the oncogenic risk of the EBDC's.

(2) Rebuttals Pertaining to Innes et al. (1969)

Both Du Pont and Rohm and Haas have challenged the results of the Innes (1969) study concerning the effects of ETU on mice, contending that the liver damage observed was the result of thyroid stress rather than the direct carcinogenicity of ETU. Du Pont (30000/18:33E) argued that the Innes study does not in itself constitute evidence that ETU is a direct liver carcinogen because the dosage used (646 ppm) undoubtedly stressed the thyroids of the mice and caused a subsequent reduction in the capacity of their livers to detoxify foreign substances, thus leading to liver damage. Rohm and Haas (30000/18:132D) likewise submitted that the test mice were hypothyroid throughout their lives as a result of ETU administration and their capacity to detoxify foreign substances was thereby reduced. Rohm and Haas argued in this connection that overloading of liver enzyme systems occurs more readily in hypothyroid animals, and that other antithyroid agents used as human drugs such as thiourea and thiouracil have been shown to increase the incidence of liver tumors in mice but not in humans.

The argument that ETU is an agent of thyroid stress and not a direct carcinogen was raised not only with Innes et al. (1969) but in connection with all three RPAR studies involving ETU, including Ulland et al. (1972) and Graham et al. (1975). The argument that the mechanism of action for ETU resembles the well-known mechanism for antithyroid drugs was, likewise, raised by Montedison in connection with Ulland et al. (1972).

Agency Finding:

Although it appears that ETU stressed the thyroid of the test mice, it has not been shown that liver tumors in the test animals result from the indirect effects of thyroid stress rather than the direct carcinogenic action of ETU. It is not sufficient to suggest that the liver damage was caused by an indirect effect of ETU. Additional data on the mechanism of action must be developed before the Agency can develop a different model to assess risk.

(3) Rebuttal Pertaining to Ulland et al. (1972)

The positive results of Ulland et al. (1972) were questioned by Montedison (30000/18:145A) on the following basis: (1) that the mechanism of action for ETU is generally recognized to be similar to the well-known mechanism for antithyroid drugs and (2) that the thyroid carcinomas observed were due not to any direct carcinogenic effect of ETU but rather to severe thyroid damage. This latter point was supported by reference to the dose-response pattern

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observed by Graham et al. (1975) as evidence that carcinomas appear exclusively as the result of thyroid damage.

Agency Finding:

The pituitary-thyroid feedback loop can be interrupted by the simultaneous administration of antithyroid agents and thyroid hormone. However, interpretation of this positive effect would require firm documentation that a full carcinogenic process is not involved. The long-term effects of coadministration have not yet been determined, and "until that has been done with ETU, one cannot rule out the possibility that the oncogenic effects on the thyroid are due to direct acting effects and not to the feedback mechanism" (Albert, November 19, 1978). It is not sufficient to suggest that the thyroid carcinomas were caused by an indirect effect of ETU. Additional studies on the mechanism of action are necessary to resolve this issue.

(4) Rebuttals Pertaining to Graham et al. (1975)

The following points of rebuttal were raised in connection with Graham et al. (1975):

- The Agency misrepresented the results of this study in PD 1.

Both Du Pont (30000/18:33E) and Rohm and Haas (30000/18:132D) pointed out that the Agency erred in stating that "thyroid carcinomas [in Graham et al. (1975)] progressed from 11 percent in the controls to 64 percent in animals fed 25 ppm ETU."

Agency Finding:

This point of rebuttal is accepted. The Agency did in fact err in representing the results of Graham et al. (1975). The incidence of thyroid carcinomas was actually 3 percent in controls (2/72 animals) and 1 percent in the 25 ppm groups (1/73 animals). The 11 percent and 64 percent figures are for the incidence of total thyroid lesions in controls and in the group fed 25 ppm, respectively (Albert 1978). A comparison of the numbers of rats with malignant tumors in control and treated groups shows that 15 of 72 controls (21 percent), 31 of 69 given 250 ppm (45 percent), and 63 of 70 given 500 ppm (90 percent) had tumors. This indicates that experimental groups had two to four times more malignant tumors than did controls (Albert 1978).

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- The study constitues evidence of an ETU no-observed-effect level (NOEL) between 25 and 125 ppm.

FMC (30000/18:10B) argued that Graham et al. (1975) clearly demonstrates that for the formation of thyroid tumors in rats a NOEL exists between 25 and 125 ppm for ETU. Du Pont interpreted the Graham study as evidence that ETU-induced tumors are not the result of single interactions of ETU with cellular tissue, but are instead the result of excessive stimulation of the endocrine organ. In addition, Du Pont (30000/18:33E) cited a long-term study conducted by Gak (1976) as evidence that concentrations of ETU less than 25 ppm were not carcinogenic to the rat.

Agency Finding:

It has not been shown conclusively that thyroid tumors in test animals result solely from the indirect effects of thyroid stress and damage. On the contrary, there is evidence that the liver and lung tumors were also induced by ETU and suggestive evidence that ETU is mutagenic (see Section II.D.5). Nor are there studies bearing on the mechanism for the induction of the liver and lung tumors by ETU. Additional data are needed to clarify the mechanism.

- Even in doses far higher than those resulting from ingesting food with ETU residues, ETU causes no irreversible damage to thyroid, pituitary, or liver.

Rohm and Haas (30000/18:132D) argued that even in doses far higher than those resulting from the ingestion of food with ETU residues, ETU causes no irreversible damage to the thyroid, pituitary, or liver.

Agency Finding:

While the doses used in the Graham study were far larger than the residues Rohm and Haas estimated to be present in the normal human diet, the Agency does not agree that the damage was reversible. Graham showed that irreversible thyroid hyperplasia occurred in rats exposed to ETU in doses ranging from 5 to 500 ppm, as Rohm and Haas acknowledged in their rebuttal. Nor is hypothyroidism a reversible condition in humans, as a study (Astwood 1960) of 230 patients with clinical hypothyroidism has shown. Conventional therapy with thyroid hormone failed to cause regression in one-third of those afflicted. Additional evidence of irreversibility of thyroid lesions is provided by the same study [illegible] that of 22 patients whose thyroids had returned to normal size after therapy, 13 patients experienced thyroid enlargement again within 6 weeks to 2 years after the termination of treatment. While these finding are not directly related to ETU-induced damage, they do show that human hypothyroidism is not a reversible condition (Albert 1979b).

- The dose-response pattern observed by Graham et al. (1975) constitutes evidence that carcinomas result solely from thyroid damage.

Montedison (30000/18:145A) argued that the dose-response pattern in Graham et al. (1975) is evidence that the carcinomas are due to severe thyroid damage rather than any direct carcinogenic effect of ETU.

Agency Finding:

Subsection II.A.2.a.(2) states the Agency's position concerning the uncertainty associated with the direct acting effects of ETU which is incompatible with this rebuttal.

b. Additional Studies Cited or Submitted in Rebuttal

(1) Additional Animal Studies Cited in Rebuttal

Several additional studies were cited or submitted to support the rebuttal argument that in well-documented chronic feeding studies, the EBDC's in contrast to ETU, have not elicited carcinogenic responses in mice, rats, or dogs.

(a) Innes et al. (1969): Maneb and Zineb

In addition to studying the effects of administering ETU in the diets of mice (646 ppm), the Innes study (1969) also tested the effects of oral administration to mice of maneb (158 ppm daily) and of zineb (1,298 ppm daily), as well as the effects a single subcutaneous injection of 100 mg maneb/kg body weight and of 1000 mg zineb/kg body weight. No significant oncogenic responses were observed in any of these tests. Du Pont (30000/18:33E) and Montedison (30000/18:145A) claimed that the Innes study thus demonstrated that maneb and zineb did not elicit carcinogenic responses in the same strains of mice administered maximum tolerated doses (158 ppm and 1,298 ppm, respectively) under the same protocols used for ETU alone.

Agency Finding:

The Agency disagrees. Maneb was given at a much lower oral dose than ETU, and thus no significant tumorigenic response was detected. Only about one-fifth of the zineb dose would have been metabolized to ETU, and the amount of ETU was far below that required to produce a detectable tumor response (Albert 1979a).

(b) Clayton et al. (1959): 2-year Rat Study

In a 2-year feeding study performed by Clayton et al. (1959), rats were fed 25, 250, and 2,500 ppm maneb. Du Pont (30000/18:33E) and Rohm and Haas (30000/18:132D) both cited Clayton et al. as a study showing a negative oncogenic reponse.

Agency Finding:

The Agency has reviewed this study and does not consider it a conclusive negative study. Definite conclusions cannot be drawn without a detailed tabulation of animal tumor and nontumor pathology and such information as survival rates, animal weights, food consumption, chemical analysis of feed to verify dose levels, and prechronic dose-finding data. Despite the fact that there were too few animals in each group, the general incidence data for all tumors in males show an increasing trend in incidence of tumors as a function of dose. The high-dose group shows a borderline statistical significance of tumor incidence as compared to the controls (Albert 1978).

(c) Blackwell-Smith (1953): Long-Term Rat Study

Rohm and Haas (30000/18:132D), FMC (30000/18:10B) and Montedison (30000/18:145A) all cited a long-term rat feeding study conducted by Blackwell-Smith that showed no relationship between treatment with zineb and the occurrence of malignancies. Lung tumors were observed in males of all groups but there was no significant difference between the controls and treated animals.

Agency Finding:

There exist statistical problems with this rebuttal attempt. There were only 10 animals in each group and 1 out of 10 animals in the control group developed tumors. Before a statistical significance would be observed, a minimum of 6 out of 10 animals in the treated group would have to develop tumors. Even if the true cancer rate in the treated group were 60 percent compared to 10 percent in the control group, the power of the test is so low that only a 66 percent chance of detecting the effect exists.- Therefore, a positive oncogenic response cannot be ruled out on such a small number of animals (Albert 1978).

(d) Blackwell-Smith 1953: Dog Study

FMC (30000/18:10B), Rohm and Haas (30000/18:132D), and Montedison (30000/18:145A) submitted this study as evidence that zineb elicited no carcinogenic responses when tested on dogs.

Agency Finding:

The study was carried out for only one year, which is not sufficient time for an oncogenic effect to develop. Blackwell-Smith reported, however, that the thyroid from the dogs that received 10,000 ppm zineb showed a hyperplastic change graded, on a scale from 0-5+, as 3+ (Albert 1978).

(2) Epidemiological Data Submitted in Rebuttal

In addition to the animal studies submitted during the rebuttal period, the Agency received epidemiological studies on the effects of EBDC's or ETU in human populations, as well as a comparison of thyroid and liver cancer mortality in areas where EBDC's are used extensively. The rebuttors argued that these epidemiological studies submitted by them prove that no hazard exists.

Agency Finding:

The registrants' efforts to provide additional information through epidemiological studies are appreciated. However, epidemiological studies are a scientific tool with a very limited power of resolution. The detectability of an adverse effect in a group of humans depends on several factors, including the duration and extent of exposure, the size of the exposed population, the detectability of the effect and the background rate of the effect.

An adverse effect can be easily missed by epidemiologic methods. Substances distributed widely in commerce or in the environment are particularly difficult to study by epidemiologic methods unless high risk ratios are observed, because it is often impossible to identify unexposed groups as controls or to separate high and low exposure groups (IRLG 1979). However, epidemiological studies can serve to confirm that risk estimates are higher or lower than those based on animal models.

(a) Epidemiological Data Submitted Concerning ETU-Exposed Rubber Workers

Du Pont (30000/18:33E) submitted two papers describing a study of thyroid cancer in rubber workers exposed to ETU through its use as a rubber accelerator (Parkes 1974; Smith 1976). The Parkes paper summarizes a study that is described in more detail in the Smith paper. The study showed no thyroid cancer in 1,929 workers in the British rubber industry.

Agency Finding:

The Agency agrees with Smith that no definite conclusions may be drawn from the study. Because of the small size of the sample, the rate of thyroid cancer would have to be greater than 100 times the background rate of 1.45 cases per 100,000 people to be detected (Albert 1979b). In addition, only thyroid cancers were considered in this study, whereas liver and lung tumors have been observed in animal studies; nor was the level of exposure to ETU measured.

(b) Epidemiological Data Submitted Concerning Factory Workers Exposed to Maneb

Du Pont (30000/18:33E) submitted a study of 635 workers at a Du Pont plant that manufactured maneb. The respondent claimed that there was only one case of thyroid cancer in this group for the period 1956 to 1977.

Agency Finding:

Two critical deficiencies are apparent in the study: (1) no control group of nonexposed workers and (2) no estimate or measurement of level of exposure to maneb. These deficiencies made it difficult to draw firm conclusions from this study (Albert 1979). In addition, as in the Smith study, only thyroid cancers were reported.

(c) Epidemiological Data Submitted Comparing EBDC Usage and Mortality Rates

Rohm and Haas (30000/18:132D) submitted comparative data on EBDC usage and mortality rates for liver and thyroid cancer in the United States. The data showed no apparent correlation between exposure to EBDC's and cancer mortality, and the respondent contended that exposure to actual residues has not resulted in adverse effects for over 30 years. Rohm and Haas used cancer mortality data compiled by the National Cancer Institute (NCI) for the years 1950 to 1969. EBDC usage data were compiled from Rohm and Haas sales statistics and from crop production maps based on data from USDA and the Commerce Department. Additionally, the respondent included a study of observed and expected mortality rates for white male workers in Washington orchards, 1950 to 1971.

Agency Finding:

Although the Rohm and Haas study showed no correlation between mortality from liver and thyroid cancer and use of EBDC fungicides, the design of the study was such that no correlation would be expected unless the use of EBDC's caused extremely severe cancer mortality. In general, the

NCI survey of mortality, by county, is difficult to interpret in terms of any single chemical. A large number of factors operate simultaneously to cause cancer mortality in the population, and additional factors affect the recording of mortality by each county. Consequently, the Agency does not consider the Rohm and Haas study a valid test of the issue it was designed to investigate, namely whether or not incidence of liver, biliary, and thyroid cancer in certain areas is related to the use of EBDC fungicides (Albert 1979a).

(d) Epidemiological Certificates Submitted Concerning EBDC-Exposed Factory and Vineyard Workers

Montedison (30000/18:145A) submitted four certificates from different organizational sources stating that no illness attributable to exposure to the EBDC's had been observed in workers in zineb production plants from 1957 to 1977 or in vineyard workers exposed to aerial application of the EBDC's.

Agency Finding:

The Agency does not agree. Although there is no reason to doubt these certified statements, definite statements cannot be made about dose-response relationships in the absence of such details as medical records and exposure data (Albert 1979a).

(3) Additional Studies Cited in Support of the Presumption

The Environmental Defense Fund (30000/18:382) cited two additional studies, Purves (1947) and Fitzhugh (1948), in support of the oncogenic activity of ETU. Both studies involved exposure to thiourea, which is structurally similar to ETU. In the study conducted by Purves (1947), rats exposed to 2,500 ppm thiourea in their drinking water developed thyroid tumors. In the study conducted by Fitzhugh, rats fed 2,500 ppm or more thiourea developed liver tumors and enlarged thyroid glands.

Agency Finding:

The Agency has reviewed these studies and concludes that, given the structural resemblance of ETU to thiourea, the reported results are consistent with the results observed for ETU.

3. Rebuttals of the Presumption of Teratogenicity

The Agency received responses from three registrants: Rohm and Haas Company (30000/18:132D), E.I. Du Pont de Nemours and Company (30000/18:33E), and FMC Corporation (30000/18:10B). The original presumption was based on evidence from three studies of teratogenic effects in laboratory animals exposed to ETU (Khera 1973; Ruddick and Khera 1975; and Kato 1976) with a margin of safety (MOS) of 250 for the population at risk from ETU. (Table II-2 summarizes the results of those three studies cited in PD 1). This MOS was calculated based on the "no observed effect level" (NOEL) of 5 mg/kg body weight found by Khera (1973) on rats. Rebuttals focused on efforts to establish a higher NOEL for ETU and the EBDC's, and to question the policy of considering ETU and all EBDC's qualitatively and quantitatively the same. (Table II-3 summarizes those studies submitted in rebuttal to the presumption of teratogenicity.)

Agency Finding:

The material submitted does not rebut the presumption of teratogenicity as applied to applicators. The general public will not, however, be at risk because of food residues of ETU. All submissions received, together with the Agency's responses, are reviewed below.

a. Additional Studies Submitted to Challenge the NOEL for ETU

Rohm and Haas (30000/18:132D) submitted a review by Gowers (1977) that represents data from additional studies on the teratogenic NOEL of ETU/EBDC's. Additionally, Rohm and Haas submitted a study by Chernoff (1977) setting a higher NOEL for ETU and maneb. Du Pont (1966) submitted proprietary data for a 3-generation reproduction study on maneb. These additional studies were submitted to establish a NOEL for ETU higher than the value of 5 mg/kg/day used to determine the MOS of 250 calculated in PD 1.

Agency Finding:

The studies submitted demonstrate that ETU and the EBDC's are teratogenic in rats. No specific teratogenic results have been observed in tests with other species, although toxic effects were frequently seen. The NOEL for ETU in rats is reported to be 5 mg/kg (Khera 1973), 10 mg/kg (Chernoff 1977), 15 mg/kg (Khera and Tryphonas, 1977), or 20 mg/kg (Lawrenz et al. 1976). No evidence was provided that negates the Khera study (1973) that showed the NOEL in rats to be 5 mg/kg/day. Because it has become common practice to make cautious and prudent assumptions wherever they are needed to conduct a risk assessment, the Agency used the 5 mg/kg NOEL found in Khera (1973) in calculating teratogenic risk (see Section II.D., "Risk Assessment").

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Table II-2. Summary of Teratogenicity Studies Cited in PD I

Compound	Author	Test Systems	Dosage	Route		Results
ETU	Khera, 1973	rat	10 mg/kg/day	M. oral[1]	+	Noel of 5 mg/kg/day used in MOS calculation
	Khera, 1973	rabbit	10 mg/kg/day	M. oral	-	No effect up to 80 mg/kg/day
	Ruddick/Khera, 1975	rat	240 mg/kg	M. oral	+	Treatment during day 10-21 of gestation, maximum effect day 12-15
	Kato, 1976	rat	100 mg/kg	S. oral[2]	+	Single treatment on day 12 of gestation

[1] Multiple oral administration

[2] Single oral administration

le II-3. Summary of Studies Submitted [illegible] ttempted Rebuttal-Teratogenicity

Reference	Species	Dose, Route	Repetitions	Remarks
		MANEB		
Du Pont (1966 (PROPRIETARY DATA)	Rat	250 ppm, diet	Three generations	No effect
Petrova-Vergieva and Ivanoba-Tchemishanska (1973)	Rat	1,000 mg/kg, oral	Day 11 or day 13	Teratogenic; no effect at 500 mg/kg
	Rat	500 mg/kg, oral	Days 2 to 21	No effect
Larsson et al. (1976)	Mouse	1,420 mg/kg, oral	Day 9 or day 13	Highest dose tested; not teratogenic
	Rat	770 mg/kg, oral	Day 11	Teratogenic; no effect at 400 mg/kg in one study; effect in another
Chernoff (1977)	Rat	480 mg/kg/day, oral	Days 6 to 20	Teratogenic; toxicity at 120 mg/kg, but not teratogenicity
	Mouse	1,200 mg/kg/day, oral	Days 6 to 15	Highest dose tested; not teratogenic
		ZINEB		
Petrova-Vergieva and Ivanova-Tchemischanska (1973)	Rat	2,000 mg/kg, oral	Day 11	Teratogenic; no effect at 1 g/kg
	Rat	4,000 mg/kg, oral	Dat 13	Teratogenic; no effect at 2 g/kg
	Rat	100 mg/m^3, 4 hr/day, inhalation	Day 5 through pregnancy	No effect; highest dose tested
		1,000 mg/kg/day, oral	Days 2 to 21	No effect; highest dose tested
				No effects (an ongoing three-generation study)
		MANCOZEB		
Larsson et al. (1965)	Rat	1,000 ppm, diet	Three generations	Not teratogenic; highest dose tested
Larsson et al. (1976)	Rat	1,320 mg/kg, oral	Day 11	Teratogenic; no teratogenicity at 730 mg/kg
Brown (1968)	Rabbit	250 mg/kg/day, oral	Days 7 to 16	Highest dose tested; no teratogenicity
		ETHYLENE THIOUREA		
Lawrens et al. (1976)	Rat	30 mg/kg, oral	Day 13	Teratogenic (unspecified effects; no effect at 20 mg/kg
Khera and Tryphonas (1977)	Rat	30 mg/kg, oral	Day 15	Teratogenic; not teratogenic at 15 mg/kg
Chernoff (1977)	Rat	20 mg/kg/day, oral	Days 6 to 30	Teratogenic; no effect at 10 mg/kg
	Rat	120.4 mg/m^3, 3 hr/day inhalation	Days 7 to 14	Toxic, but no teratogenicity
	Mouse	200 mg/kg/day, oral	Days 6 to 15	Highest dose tested; toxic to liver, but not teratogenic
Lu and Staples (1978)	Rat	40 mg/kg/day gavage	Days 7 to 15	ETU induced terata, but not via alteration of maternal thyroid status
Emmerling (1978)	Rat	40 mg/kg/day gavage	Days 7 to 20	Incidence of terata reduced when hormones were administered with the lower dose of ETU (20 mg/kg).

b. Additional Studies Submitted in Rebuttal: Mancozeb

Rohm and Haas (30000/18:132D) claimed that mancozeb had no teratogenic effect in rats administered 100 mg/kg (Larsson, 1976; unpublished) and that earlier studies conducted for their company have shown no effects at even higher doses in test animals (Brown 1968, in rabbits; Larsson et al. 1965, in rats). Rohm and Haas further argued that the fact that mancozeb is metabolized in part to ETU and that mancozeb is "inactive in the rat" provided further evidence that ETU, as it occurs in the mancozeb residue, does not present a teratogenic hazard. Consequently, the commentor stated that this compound should be considered separately from other EBDC's.

Agency Finding:

The Agency acknowledges that the Rohm and Haas studies did not show teratogenic effects with mancozeb at the same level as ETU did. In particular, a reproductive study of three generations of rats showed no effects at the highest dose (1,000 ppm in the feed) (Larsson 1965). A second study showed no teratology in rabbits when 250 mg/kg/day mancozeb was administered on days 7 through 16 of gestation (Brown 1968). In a third study (Larsson 1976), the effects of mancozeb and maneb were compared. The NOEL for mancozeb in rats was 730 mg/kg on day 11; for maneb the NOEL was 400 mg/kg on day 11.

The studies outlined above and in Table II-3 show that mancozeb's teratogenic potency in rats is similar (NOEL within a factor of 2) to that of maneb and zineb and much less than that of ETU. In addition, neither mancozeb nor ETU were teratogenic in rabbits--only in rats. Therefore, mancozeb has been grouped qualitatively with the other EBDC's (i.e., maneb and zineb) which is based on the teratogenic risk assessment on ETU exposure and ETU NOEL.

c. Additional Studies Submitted to Establish Teratogenicity as an Indirect Effect

Rohm and Haas (30000/18:132D) claimed that laboratory evidence they have submitted in rebuttal establishes "beyond a doubt" that the teratogenic effect of ETU in the rat is mediated through an induced deficiency of thyroid hormones, in particular triiodothyronine (T_3)and thyroxine (T_4) and that, therefore, ETU does not have a direct teratogenic effect on the fetus. The evidence submitted consisted of a teratogenic study of ETU in rats (Lu and Staples 1978) and a study of the effects of thyroid hormones on the teratogenic potential of ETU conducted for Rohm and Haas (Emmerling 1978).

Agency Finding:

The two studies do not support the Rohm and Haas claim. Although the Emmerling study does show that the incidence of several defects is significantly reduced when T_3/T_4 is coadministered with the lower dose of ETU (20 mg/kg), the administration of thyroid hormone does not completely block the teratogenic effect of ETU. The study thus fails to establish that the teratogenic effect of ETU is mediated solely through thyroid inhibition. Moreover, the study by Lu and Staples fails to demonstrate any decrease in the teratogenicity of ETU when T_4 is administered simultaneously. ETU increased the incidence of malformations in fetuses in dams that were thyroparathyroidectomized, indicating that the presence of an active thyroid is not required for ETU to be teratogenic.

These studies do not support the rebuttal issue of an indirect teratogenic effect of ETU via thyroid inhibition. It should be stressed also that attempting to explain the mechanism of action of a teratogen (e.g., maternal thyroid inhibition) does not alter the teratogenic potential of a chemical. A chemical acting either directly or indirectly as a teratogen may be a hazard to human fetal development.

d. Epidemiological Data Submitted in Rebuttal: ETU

Du Pont (30000/18:33E) submitted a study of teratogenic effects in female workers in the British rubber industry who had been exposed to ETU through its use as a rubber accelerator. A review of birth records for 420 babies born to 255 mothers revealed no greater incidence of birth defects in the exposed population than in the general population of Birmingham, the city of study (Smith 1976).

Agency Finding:

The information provided by this study is inadequate to judge its validity. A number of questions remain unanswered, such as whether the incidence in the general population was calculated with or without inclusion of the 255 exposed women. Comparison with a cohort outside of Birmingham might strengthen this claim since it is not known whether the general population was exposed to ETU in air or drinking water. This study did not provide sufficient data on which to base any conclusions about the teratogenic effects of ETU in humans.

B. Comments and Information Submitted on Other Possible Adverse Effects

In addition to the presumptions of acute toxicity to aquatic organisms, oncogenicity, and teratogenicity, in PD 1 the Agency identified three possible adverse effects of the EBDC's and requested additional evidence. The effects in question were thyroid aberrations, mutagenicity, and skin sensitization. The Agency has reviewed all material available and concludes that the RPAR risk criteria for thyroid effects and mutagenicity have been met. With regard to skin sensitization as a possible adverse effect of EBDC's, the Agency concludes that although the EBDC's are skin sensitizers, no risk criterion has been met.

1. Thyroid Aberrations as a Possible Adverse Effect

The Agency received responses from three registrants: Rohm and Haas (30000/18:132D), FMC (30000/18:10B), and Montedison (30000/18:145A). The submissions were addressed primarily to the issues of establishing NOEL's so that margins of safety (MOS) could be calculated and defining the mechanism of action of thyroid toxicity caused by ETU (Sandusky 1978). The Agency's original concern was primarily based on a study by Freudenthal (1977) that indicated that ETU produced definite thyroid toxicity (hyperplasia) in rats at doses above 25 ppm in the feed (0.24 mg/kg/body weight). Graham et al. (1975) also reported a NOEL of 25 ppm for thyroid effects in rats. Although the results of the Freudenthal study were available when PD 1 was issued, the Agency had not performed an evaluation of the study and, therefore, did not consider a rebuttable presumption justifiable at that time.

Agency Finding:

Having evaluated Freudenthal (1977), reviewed the comments and additional studies (Table II-4) submitted during the rebuttal period, and having considered the exposure to ETU as a result of EBDC use, the Agency concludes that the EBDC's pose a risk that exceeds the criterion for adverse thyroid effects.

a. Comments and Additional Studies Submitted on Behalf of NOEL's

Three registrants submitted comments concerning the NOEL's for the EBDC's and ETU: Du Pont (30000/18:33E), FMC (30000/18:10B) and Rohm and Haas (30000/18:132D). To establish a NOEL for ETU, the Agency sponsored a 5-month feeding study on rhesus monkeys (Leber et al. 1978a). The Agency finds these studies collectively adequate, within the bounds of experimental design, to establish NOEL's for the EBDC's and ETU. (See Subsection II.D., "Risk Assessment.")

Du Pont (30000/18:33E) concurred with the 25 ppm NOEL in rats reported for ETU by Freudenthal (1977) and maintained

Table II-4. Summary of Studies Relating to Thyroid Effects

Compound	Author	Test	Results
ETU	Freudenthal (1977)	90-day rat feeding	Effective = 25 ppm; enlarged, red thyroids
	Graham et al. (1975)	2-yr. rat feeding	NOEL = 25 ppm for thyroid.
	Leber et al. (1978a)	5-mo. rhesus monkey feeding	NOEL = 10 ppm.
	Rohm and Haas (Leber, 1978)	4 1/2 and 12-wk. rat feeding	No NOEL was estimated. Thyroid status returned to normal 2-4 weeks after cessation of treatment.
	Gak (1976)	2-yr. rat feeding	NOEL = 17 ppm.
	Gak (1976)	20-mo. hamster feeding	Increased thyroid weight at highest dose but no morphological pathology.
MANEB	Clayton (1957)	2-yr. rat feeding	NOEL = 250 ppm or 12 mg/kg/day.
ZINEB	Montedison	Certificates stating that in 20 yrs. of manufacture there were no thyroid abnormalities	Not valid -- no medical records, exposure measurements provided.
MANCOZEB	Rohm and Haas Leber (1978)	12-wk. rat feeding	Reversibility of thyroid effects at doses of 625 & 1250 ppm.
	Rohm and Haas Two Studies	Epidemiological	Negative -- exposure not measured concurrently with the study, but most complete study to date on on human population.
	Gordon (1978) Braverman (1978)		

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that this indicates a sufficient MOS to permit use of EBDC's on crops without significant risk of thyroid dysfunction. Du Pont also cited a long-term feeding study in rats (24 months) and hamsters (200 months) that showed that the NOEL for rats is 17 ppm (Gak 1976). The hamster, however, was much less sensitive to ETU than the rat. The highest dose administered to the hamster (200 ppm) produced an increase in weight but not morphologic pathology.

FMC (30000/18:10B) submitted an 8-week feeding study in rats at 25 ppm ETU. The only effect observed in this study was reduced thyroid weight. In contrast to the Freudenthal (1977) and Graham (1975) studies, no enlargement of the thyroid or hyperplasia was recorded at this level.

Rohm and Haas (30000/18:132D) sponsored and submitted a feeding study conducted by Leber et al. (1978) on rats with ETU and mancozeb. The effects with 625 ppm mancozeb were similar to those with 125 ppm ETU. This particular study did not establish a NOEL for ETU on rats.

Agency Findings:

A 5-month feeding study on rhesus monkeys, conducted for EPA by Leber et al. (1978a), established the NOEL for ETU in monkeys at 10 ppm. The studies submitted by the registrants, together with this Agency-sponsored study, clearly demonstrate the differences in various species' susceptibilities to thyroid effects. Several other factors may also complicate the establishment of a reliable NOEL, e.g., normal compensatory mechanisms, dietary iodine levels, and individual variations. Data from these studies are sufficient, however, to establish NOEL's for the EBDC's and ETU. (NOEL's and margins of safety for human exposure are addressed in Subsection II.D, "Risk Assessment.")

b. Additional Studies Submitted on the Mechanisms of Actions of Thyroid Toxicity

Comments on the mechanism of action of EBDC/ETU-induced thyroid toxicity were submitted to the Agency by Rohm and Haas (30000/18:132D). The registrant submitted an extensive review by Gowers (30000/18:132D) that argued that prolonged exposure to ETU inhibits the production of thyroid hormone. This hormone imbalance leads to increased levels of the thyroid-stimulating hormone (TSH) from the anterior pituitary. Prolonged, elevated levels of TSH result in overstimulation of the thyroid gland, eventually causing hyperplasia.

This type of feedback hyperplasia is well documented and backed by extensive experimental evidence. The Agency, therefore, concurs with the position taken by Rohm and Haas. The standard antithyroid agents in medical practice, like ETU, are thiourea derivatives. It is reasonable to assume that the mechanism of ETU-induced thyroid toxicity is mediated through the feedback control system described above.

Rohm and Haas (30000/18:132D) maintained further that thyroid hyperplasia is a reversible effect if the stimulus is removed soon enough. In Leber et al. (1978), a rebuttal study mentioned in Subsection II.B.1(a) above, rats were fed ETU for 12 weeks (625 ppm) and thereafter fed control feed for up to 10 weeks. All thyroid effects returned to normal two to four weeks after cessation of treatment. Concomitant administration of thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) delayed the appearance of the effects.

Rohm and Haas (30000/18:132D) pointed out that when the rats were fed mancozeb instead of ETU for 12 weeks at doses of 625 or 1,250 ppm, the results showed reversibility of the antithyroid effects. The effects with 625 ppm mancozeb were similar to those with 125 ppm ETU (Leber et al. 1978).

Agency Finding:

The Agency agrees that the hyperplasia might be a reversible process. However, during the period of inhibition of the thyroid function, exposed populations may still be subject to the risk and complications of thyroid hyperplasia. Furthermore, evidence from clinical human studies indicates that therapy of hypothyroidism failed to cause regression in one third of treated patients (Astwood 1960). Therefore, the Agency is concerned about the uncertainty regarding the time of transition from reversibility to irreversibility and whether the hyperplasia is completely reversible.

c. Data Submitted Concerning Mancozeb-Exposed Factory Workers

(1) Rohm and Haas Rebuttals

Rohm and Haas [30000/18:132D and 132G (Confidential)] submitted two epidemiological studies of workers employed in a mancozeb plant. Although the presence of ETU in the urine of the workers confirmed their exposure to EBDC's, no unequivocal evidence of thyroid toxicity was found.

The more extensive of the two studies [30000/18:132G (Confidential)] consisted of two experimental groups: 41 workers involved in mancozeb production during the study and 112 workers who had been in mancozeb production at some previous time. The first group had spent 0.5 to 25.6 years on the job. The second group had been exposed from 0.9 to 16.2 years. A control group for each experimental group was matched by sex, age, race, and time of employment. Forty-three clinical chemical measures on urine and blood from these workers were performed. Hormone analyses of thyroid function included the thyroid hormones T_3 and T_4 and the thyroid-stimulating hormone released by the pituitary. Analysis of the data failed to show any work-related increase in thyroid pathology.

Agency Finding:

Although this was one of the best epidemiological studies received by the Agency and is the most complete study to date of EBDC effects in a human population, neither exposure to mancozeb nor the other EBDC's were quantitatively measured at the time of the study. The study thus provides qualitative data but is not adequate for quantitatively assessing risk.

(2) Montedison Rebuttal

Montedison (30000/18:145A) submitted epidemiological certificates that testified that in 20 years of zineb manufacturing, workers exhibited no thyroid abnormalities.

Agency Finding:

The lack of information on thyroid abnormalities during these twenty years may be due to the unavailability of medical records, exposure measurements, or any other pertinent details (Albert 1979). No definite conclusions can be based on them.

2. Comments Submitted and Additional Studies on Mutagenicity as a Possible Adverse Effect

The Agency received responses from two registrants: Rohm and Haas and Du Pont. The Agency's original concern was based on six studies in which the mutagenic effects of maneb, zineb, and ETU were investigated. Three of the studies (Antonovich 1974; Pilinskaya 1974; Slifkin 1973) tested the mutagenic effects of the EBDC's. The remaining three studies (Seiler 1974; Teramoto 1977; Seiler 1975) examined the mutagenic effects of ETU (Tables II-5(a) and II-5(b)).

Of the three EBDC studies, two were Russian studies that reported increased frequencies of chromosomal aberrations in cultured human lymphocytes treated with maneb or zineb, and in rabbits or mice treated orally with maneb or zineb (Antonovich 1972; Pilinskaya 1974). The third EBDC study found aberrant colonies in the phytopathogenic fungus *Alternaria mali* exposed to several EBDC's (Slifkin 1973).

The studies involving ETU showed weak positive activity without metabolic activation in microbial systems used to detect base substitution mutations *S. typhimurium* strains

Table II-5 (a). Summary of Mutagenicity Studies on ETU from PD 1 and Rebuttal Submissions

Author	Test	Species	Results
ETU			
Seiler (1974)	Ames	*S. typhimurium* G-46	Positive without metabolic activation for bacterial systems (TA-1535, GA-46.
	Ames	*S. typhimurium* TA-1530, 1531, 1532, 1534	Inconclusive with or without metabolic activation.
Teramoto (1977)	Ames	*S. typhimurium* TA-1535	Positive
	Ames	*S. typhimurium* G-46, TA-1536, TA-1537, TA-1538, *E. coli* WP2	Negative
	Cytogenetic	Chinese hamster DON cells *in vitro*	Negative
	Cytogenetic	Mouse bone marrow *in vivo*	Negative
	Dominant lethal	Mouse	Negative
Seiler (1975)	Cytogenetic (N-nitroso-ETU)	Mouse bone marrow	Positive
Von Meyer (1977)	Ames	*S. typhimurium* TA-100, TA-1535	Marginally Positive
	Ames	*S. typhimurium* TA-1537, TA-1538, TA-98	Negative
Shapiro (1977)	Ames	*S. typhimurium* TA-1535, TA-100, TA-1537, TA-98	Negative
Newton (1977)	Cytogenetic Anal.	Rat lymphocyte *in vivo*	Negative
Austin (1977)	DNA binding	Rat liver DNA	Negative
Schupbach and Hummler (1977)	Ames	*S. typhimurium* TA-1530	Positive
	Host-mediated	Mouse/G-46	Negative
		Mouse/TA-1530	Inconclusive
Shirasu (1977)	Host-mediated	Rat, Mouse/G-46	Negative
	Ames	*S. typhimurium* TA-1535	Positive
	Cytogenetic	Rat bone marrow *in vivo*	Negative

Table II-5 (b). Summary of Mutagenicity Studies on EBDC's From PD-1 and Rebuttal Submissions

Author	Test	Species	Results
MANEB & ZINEB			
Antonovich (1972)	Cytogenetic	Rabbit bone marrow *in vivo*	Positive for maneb; Negative for zineb
	Cytogenetic Anal.	Mouse bone marrow *in vivo*	Positive for maneb; and zineb
	Cytogenetic	Human blood lymphocytes, *in vitro*	Positive for maneb and zineb
MANEB			
Seiler (1973)	Ames	*S. typhimurium* TA-1532, TA-1534	Weakly, positive without metabolic activation
		S. typhimurium G-46, TA-1520,	Negative
ZINEB			
Slifkin (1973)	Point mutations	*Alternaria mali*	Positive
Mollet (1974)	Sex linked recessive lethal	*Drosophila melanogaster*	Negative
Pilinskaya (1974)	Cytogenetic	Mouse bone marrow *in vivo*	Positive
Pilinskaya (1974)	Epidemiological Data	Human blood lymphocytes/cultures	Positive
Benes and Sram (1969)	Sex linked recessive lethal	*D. melanogaster*	Negative
MANCOZEB			
Newton (1977)	Cytogenetic	Rat lymphocyte *in vivo*	Positive at highest dose

G-46 and TA 1535 (Seiler 1974; Teramoto 1977). The combination of ETU with sodium nitrite to form N-nitroso ETU resulted in increased mutagenic activity in both microbial and mammalian systems (Seiler 1975).

Based on the following review of the rebuttal comments, company submitted studies and studies available in the published literature or reported from national and international testing programs since PD 1, the Agency concludes that the EBDS's have inadequately tested and , therefore, the evidence for the EBDC's is inconclusive. However, the evidence for ETU meets the 40 CFR 162.11 risk criterion of multitest evidence for possible mutagenicity in microbial systems. These data are further evaluated in Section II.D.5. The Agency's conclusions on the potential mutagenicity of the EBDC's and ETU are presented on that section.

a. Comments Submitted on Mutagenicity Studies Cited as Original Bases for Concern

Two registrants, Rohm and Haas (30000/18:132D) and Du Pont (30000/18:33E), submitted comments on the studies cited in PD 1. Comments focused on the relevance of test results in microbial systems, on the use of DMSO as a solvent, and on the interpretation of results of the Pilinskaya (1974) study.

(1) Comments Submitted on the Significance of Results in Microbial Systems

Du Pont (30000/18:33E) questioned the significance of positive results in microbial tests unless those results are supported by information from other kinds of tests. Rohm and Haas (30000/18:132D) questioned results from culture systems on the basis that the normal nutritional and supportive environment of the parent animal is lacking, and cell cultures do not have mechanisms for excretion and detoxification.

Agency Finding:

Nonhuman test systems are considered by the Agency in determining the mutagenic potential of chemicals. Microbial test systems offer advantages in predicting genetic events because of their high sensitivity of these systems, the ease and speed of conducting the tests, the low cost, and the large data base. Moreover, the use of a mammalian activation system allows the microbial test to determine the mutagenic potential of the metabolic products of the test chemical that are likely to be present in the mammalian system. Cell culture systems provide relevant information on the mutagenic potential of a chemical substance because the organization of the chromosomes and the DNA content is the same for both *in vitro* and *in vivo* cells. Although *in vitro* cells lack the tissue organization, detoxification, and waste excretion systems of the *in vivo* system, this drawback only limits the development of quantitative estimates of mutagenic potential from the *in vitro* data and does not detract from the qualitative value of the information.

(2) Comments Submitted on the Use of the Solvent DMSO in Mutagenicity Testing

Rohm and Haas (30000/18:132D) questioned the validity of Seiler (1974) because DMSO was used as solvent for ETU. The registrant contended that the results from such studies are questionable because DMSO can pass through cell membranes and it inhibits enzymes important to normal cell metabolism.

Agency Finding:

The Agency disagrees. The Agency has found no reports indicating that DMSO is mutagenic at the concentrations customarily employed in such tests. DMSO has been validated in the Ames test and is one of the most commonly used solvents in this test system. Although DMSO can affect the *in vitro* culture conditions or membrane integrity, the use of this dispersal agent does not invalidate the results of the study. In the absence of data to suggest a biochemical problem that could influence the expression of mutagenic potential, this vehicle is considered an appropriate solvent. Because ETU is only moderately soluble in water, the fact that ETU dissolved in water produced negative results (in contrast to the positive results produced by ETU dissolved in DMSO) cannot be used as an argument that DMSO is mutagenic (Schupbach and Hummler 1977).

(3) Comments Relating to Pilinskaya (1974)

Pilinskaya (1974) examined human lymphocytes cultured from 15 workers who were employed in various parts of a zineb manufacturing plant. A significantly higher rate of aberrant metaphases was observed in these workers than in the controls. Rohm and Haas (30000/18:132D) suggested that the chromosomal aberrations observed in the Pilinskaya study were linked to the "well known allergenic property of zineb."

Agency Finding:

The Agency disagrees. A literature search was performed to locate studies that could support the registrant's argument, but the Agency was unable to find any indication that chromosome aberrations are associated with an allergic response (Anderson 1979b).

b. Additional Studies Submitted as Evidence Against Mutagenicity

Rohm and Haas (30000/18:132D) submitted four additional studies (Von Meyer 1977; Shapiro 1977; Newton 1977; Austin 1977) to support the argument that ETU is not mutagenic and that ETU is in fact incapable of binding or interfering with DNA. These studies are summarized in Table II-5(a).

c. Additional Agency Findings Concerning Mutagenicity

After the publication of PD 1, the Agency uncovered several additional studies of the mutagenic effects of ETU: Schupbach and Hummler (1977), Shirasu (1977), Seiler (1977), Benes amd Sram (1969) and Mollet (1974). These are summarized in Tables II-5(a) and (b).

d. Recent Mutagenicity Testing of ETU (The International Collaborative Program (1981))

ETU was among 42 coded chemicals evaluated for mutagenicity in a large number of assays by participants in the International Collaborative Program:* "Evaluation of Short-Term Tests for Carcinogens" (1982). Using aliquotes of the same re-purified sample, over 60 laboratories tested ETU in their own variations of test protocols for bacterial repair and gene mutation; in yeast assays; for *in vitro* mammalian repair, gene mutation and chromosome aberration, as well as for cell transformation; and in *in vivo* assays (Table II-5(c)). *In vitro* assays were performed with and without mammalian metabolic activation provided by rat hepatic microsomal preparations (S-9). Although almost a quarter of these laboratories (15/61) reproted ETU as mutagenic, a majority of these results (12/15) were registered in microbial systems. The only significant positive mammalian result was the singular direct activity (i.e., without metabolic activiation) in HeLa cell unscheduled DNA synthesis (UDS). Notably, confirmed positive results were also reported for BHK-21 cell transformation from two laboratories (with/without rat S-9 activation). Finally, at intraperitoneal doses approaching the LD-50 in mice, only one of 3 assays for micronuclei was inconclusively "positive," whereas tests for sister-chromatid exchange (SCE) and abnormal sperm morphology were negative. These results are consistent with negative results previously reported in mammalian systems. The only assay for sex-linked recessive lethals in Drosophila performed

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*None of the EBDC's were tested in this program.

Table-II-5 (c). International Collaborative Program (1981): Tabulation of Results (Mutagenicity) - ETU

ASSAY GROUP	Organism (Cell)/Test	LABORATORY													Assessment (No. of):		
		1	2	3	4	5	6	7	8	9	10	11	12	13	+	-	(±)
I.	**Bacterial Repair/Ancillary Assays:**																
	Bacillus subtilis/rec	+													1		
	Escherichia coli/rec/PolA	-	+	-	+										2	2	
	E. coli lambda/Inductest	+													1		
	Rat liver Degranulation (hormone assay)	-	-													2	
	Human Fibroblasts/Nuclear Enlargement	-														1	
	HeLa/Nuclear Enlargement	+													1		
II.	**Bacterial Mutation Assays:**																
	Salmonella (Ames)/his	-	-	+	-	-	-	-	(±)	-	-	-	+	-	2	10	1
	E. coli/try	-	-	+	-	-	-	-							1	6	
III.	**Yeast Assays:**																
	Saccharomyces/gene mutation	-	+												1	1	
	S. cerevisiae/aneuploidy	+													1		
	S. cerevisiae/recombination	+	-	-	-	+									2	3	
IV.	**In vitro Mammalian Assays:***																
	WI-38/UDS	-	-													2	
	HeLa/ UDS	+													1		
	CHO / SCE	-	-	-												3	
	CHO / CA	-														1	
	RL-1/ CA	(±)															1
	L5178Y/TK	-														1	
	CHO / HGPRT	-														1	
	CHO / APRT	-														1	
	CHO / OUA-r	-														1	
	CHO / FUdr-r	-														1	
	BHK-21/ Transf.	+	+												2		
	C3H-MLV/Infect.	-														1	
V.	**In vivo Assays:****																
	Drosophila/ SLRL	-														1	
	Mouse /SCE (ip)	-														1	
	Mouse /MT (ip)	(±)	-	-												2	1
	Mouse/Sperm Morph.	-	-													2	

Footnotes (to Table II-5(c))

*WI-38/UDS - unscheduled DNA synthesis in human fibroblasts

HeLa/UD - unscheduled DNA synthesis in human lung cell line

CHO/SCE - sister chromated exchange in Chinese hamster ovary cells

CHO/CA - chromosome aberration in Chinese hamster cells

RL-1/CA - chromosome aberrations in rat liver cells

L5178Y/TK - gene mutation at the thymidine kinase locus in mouse lymphoma cells

CHO/HGPRT/APRT/OUA-r/FUdr-r - gene mutation at the hypoxanthine quanine phosphoribosyl transferase, adenine phophoribosyl transferase, ouabain and fluorodesyurdine loci in Chinese hamster ovary cells

BHK-21/TRANSF - transformation in baby hamster kidney cells

C3H-MLV/INF - enhancement of mouse leukemia virus activation in prophage infected mouse cells

**Drosphila/SLRL - sex-linked recessive lethals indirection in Drosophila melanogaster

Mouse/SCE (ip) - indirection of sister chromated exchange in mice treated ip

Mouse/MT (ip) - micronulei test in mice treated ip

Mouse/Sperm Morph - abnormal sperm morphology in mice

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with ETU for this program was also negative, confirming previous evaluations in this assay system.

e. Recent Mutagenicity Testing of the EBDC's and Additional Studies on ETU (Published Literature/Testing Programs)

(1) ETU

Recent studies with ETU, not considered in PD-1, have beeen obtained (Table II-5(d)). The results of this set of studies do not alter the general assessment generated by the International Collaborative Program, other than to bolster the number of negatives for mammalian *in vivo* testing (in the mouse micronucleus test, and for rat lymphocyte cytogenetics), as well as to reaffirm the ability of the chemical to transform Syrian hamster embryo cell cultures.

(2) EDA

A single assay has been reported with ethylene diamine (EDA), an acid-derived metabolite of both the EBDC's and ETU. EDA is also a starting component in the synthesis of most commercially available EBDC's. Larval treatment of *Drosophila melanogaster* to detect sex-linked recessive lethals was negative (NTP, 1982). No mutagenicity testing of any other metabolite, derivative, contaminant or degradation product of either the EBDC's or ETU has come to light.

(3) EBDC's

As footnoted above, none of the EBDC's were assayed for mutagenicity in the International Collaborative Program. However, over 40 short-term mutagenicity studies have been reported (either published or from other testing programs) since the initial RPAR assessment of these fungicides. The majority (37 of 46) listed in Table II-5(d) have been performed with the three most widely used EBDC's, mancozeb, maneb and zineb (about a dozen studies each). By contrast, nabam is represented by only one assay (plant cytogenetics), and amobam by none. When accumulated by assay type group (microbial, in vitro mammalian, etc.), this data set appears to represent a respectable degree of testing. However, each of the EBDC's is represented most often by single, unconfirmed reports for each specific test, particularly for mammalian assays. (See Table II-5(d).) Additionally, it must be noted that the quality of this data base (as with the previous data discussed in PD-1) has not been critically evaluated independently by the Agency.

Except for nabam and amobam, which have not been tested, the overall results reported (Table II-5(d)) appear to indicate that none of the EBDC's has any apparent mutagenic

Table-II-5 (d). Summary of Testing [illegible]'s for Mutagenicity Since PD-1

ASSAY SYSTEMS (BY GROUP & TEST TYPE)

EBDC	Plant	Bacterial					Yeast/Fungal					In vitro Mammalian						In vivo				SOURCE
	ALC CA	Ames (his)	E.coli (try)	B.subtil. (his/met)	E.coli (REP)	B.subt (REP)	Sac.D3 (MCO)	Sac.D4 (GC)	Sac.D7 (GC/CO)	ASN (AN)	ASG (CO)	WI-38 (UDS)	BHK (TR)	SHE/SA7 (TRANS)	Rat Thymo (DNA-INH)	Hum.Lymph (UDS)	V79 (CA)	Droso. (SLRL)	Rat BM (CA)	Rat Lymph (CA)	Mouse (MT)	(Reference)
MANEB								-/-														EPA Gene-Tox, 1980
		-/-	-/-		-/?	-/?	+(±					-/-										SIR, 1979
		-/-				+/?											+/-		-			Kawachi et al., 1980
															+/NT	+/NT						Rocchi et al, 1980
MANCOZEB		-/-	-/-		-/?	-/?	+/+					-/-										SRI, 1979
		-/-	-/-			-/-																Shirasu et al., 1979
																		-				Vasudeu and Krithnamurthy, 1980
									-/?													EPA Gene-Tox, 1982
																				+		Newton, 1979
METIRAM		-/-	-/-		-/?	-/?	-/-					-/-										SRI, 1979
								+/?	-/-													EPA Gene-Tox, 1982
NABAM	+/+																					EPA Gene-Tox, 1982
ZINEB		-/-	-/-		-/?	-/?	+/+					-/-										SRI, 1979
				+/+																		Shiau et al., 1980
															+/NT	+/NT						Rocchi et al., 1980
								+/?		-/-	-/-											EPA Gene-Tox, 1982
ETU		NT/+																				Anderson & Styles, 1978
														+/NT								EPA Gene-Tox, 1982
													-/+									Styles, 1978
																					-	Jensson and Ramel, 1980
																				-		Newton, 1979

Footnotes:

In vitro Studies: Results reported without/with rat S-9 metabolic activation system e.g., -/-). NT, not performed; ?, not reported (= not tested?); (±), inconclusive.

Test Code: ALC/CA, chromosome abberations in Allium cepa root tip cells.
Ames/(his), reverse gene mutation in one or more of Ames Tester Strains (TA series), auxotrophic for histidine.
E.coli/(try), reverse gene mutation in trypotophan auxotroph of Escherichia coli.
B.subtil/(his/met), reverse gene mutation in the histidine/methionine auxotrophic strain TKJ6321 of Bacillus subtilis.
E.coli/(REP), differential toxicity (repair) in isogenic repair strains (proficient/deficient) of Escherichia coli.
B. subt/(REP), differential toxicity (repair) in strains of B.subtilis.
Sac. D3/(MCO), mitotic crossing over in the D3 strain of Saccharomyces cerevisiae.
Sac.D4/(GC), gene conversion in the D4 strain of S.cervisiae.
Sac.D7/(GC/CO), gene conversion/crossing over in the D7 strain of S. cerevisiae.
ASN/(AN), aneuploidy in Aspergillus nidulans.
ASG/(CO), crossing over in A.nidulans.
WI-38/UDS, unscheduled DNA synthesis in the human embryonic fibro-blast cultured cell, WI-38.
BHK/(TR), transformation in the baby hamster kidney cell line, BHK-21.
SHE/SA7/([illegible] transformation in Syrian hamster cell infected with the simian adenovirus, SA-7.
Rat thy[illegible] inhibition of scheduled (main) DNA synthesis in cultured rat thymocytes.
Hum.Lymph/(UDS), unscheduled DNA synthesis (repair) in human lymphocytes cultures in vitro.
V79/(CA), chromosome aberrations in the Chinese hamster lung cell line, V79.
Droso/(SLRL), sex-linked recessive lethals in Drosophila melanogaster.
Rat BM/(CA), chromosome aberrations in (treated) rat bone-marrow preparations.
Rat Lymph/(CA), chromosome aberrations in (treated) rat lymphocytes.
Mouse/(MT), micronuclei in bone marrow smears of (treated) mice.

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activity in the majority of assays for bacterial mutation or repair (20 negative of 22 conducted). The exceptional positives were recorded for zineb in both activated (rat S-9) and unactivated cultures of B. subtilis, strain TKJ6321 (Shiau et al. 1980), and for maneb in one B. subtilis repair test. On the other hand, recombination assays using strains of the yeast Saccharomyces cerevisiae (D3, D4, D7), which detect mitotic crossing over and/or gene conversion, recorded positive results for the most part (6 or 9 studies), irrespective of the test chemical or the presence or absence of a metabolic activation system. This is not unexpected, since these fungicides have a wide spectrum of activity. The two Aspergillus tests performed with zineb (for aneuploidy and corssing-over), however, were negative, which would indicate either selective resistance, or inadequate testing.

Whereas none of the EBDC's increased unscheduled DNA synthesis in WI-38 cells (human fetal fibroblasts), an Italian study (Rocchi et al. 1980) reported both maneb and zineb inhibited scheduled (i.e., main) DNA synthesis in rat thymocyte cell cultures. Maneb and zineb also caused elevated repair synthesis (induced UDS) in human lymphocytes (no tests were performed with metabolic activation). In addition, there is a single report on maneb clastogenicity (chromosome breakage) in V79 Chinese hamster lung cells (Kawachi et al. 1980).

Two of the three in vivo studies of this recent EBDC data set reported negative results: A Drosophila assay for sex-linked recessive lethals with mancozeb (Vasudev 1980); and a rat bone-marrow cytogenetic study with maneb (Kawachi et al. 1980). The third study (Newton 1979) evaluated the clastogenic potential of mancozeb and ETU administered both intraperitoneally and by gavage to rats (age, sex and strain not reported) at acute doses between 3 and 50 mg/kg (the highest dose approximated an LD-0.3 for the EBDC, and an LD-1.4 for ETU). The investigator reported slight but significant increases over solvent controls (p less than 0.005) in the number of chromosome aberrations per cell in rat lymphocyte cultures established from mancozeb-treated animals (for both routes of administration), but not from animals given ETU (either route). On the basis of these results, Newton suggested that the clastogenic activity of mancozeb cannot be related to the formation of ETU (at least in the rat), but may reside in the whole molecule, or be due to the release of manganese ions (Mn) from the mancozeb. In contrast to zinc ions, Mn has been shown to be "mutagenic" in a number of yeast systems detecting DNA repair and/or chromosome aberrations (references in Newton, 1979).

3. Comments and Additional Studies Submitted on Skin Sensitization as a Possible Adverse Effect

The Agency received comments from two registrants, Rohm and Haas (30000/18:132D) and Du Pont (30000/18:33E).

Agency Finding:

EBDC's are potential skin irritants but probably not strong sensitizers. No risk criterion warranting a rebuttable presumption has been met for skin sensitization.

(a) Comments Submitted on Skin Sensitization Studies Cited as Original Bases of Concern

In PD 1, the Agency cited three studies that indicated that the EBDC's might pose a skin sensitization risk: Zotin (1970), Matsushita et al. (1976), and Clayton (1957). The Agency received comments on the Zotin and Clayton studies but not on the Matsushita study of the skin sensitization effects of the EBDC's on female guinea pigs. At the time PD1 was published, the Agency had reviewed the latter study only in abstract form.

Agency Finding:

The Agency has reviewed Matsushita et al. and concludes that mancozeb, maneb, and zineb produce cross-sensitization in guinea pigs, but that ETU does not produce sensitization as readily as the EBDC's themselves. However, the Agency considers this study a case report only, since skin sensitization is one of the few phenomena in toxicology that can be and usually is experimentally evaluated directly in man (Woodard 1979).

(1) Comments Pertaining to Zotin (1970)

Zotin (1970), a study conducted in the Soviet Union, reported contact dermatitis in 86 farmworkers exposed to zineb. Rohm and Haas (30000/18:132D) and Du Pont (30000/18:33E) pointed out that this study involved a formulation of zineb not produced in the United States. The implication was that chemicals other than zineb might have triggered the reported instances of dermatitis.

Agency Finding:

The study performed by Zotin was inconclusive in that no data concerning impurities were provided (MRI 1978).

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(2) Comments Pertaining to Clayton (1957)

Clayton (1957), which reported skin sensitization in male guinea pigs to which a 20-percent water suspension of maneb was applied, was originally submitted by Du Pont in connection with tolerance requests (PP 156).

Du Pont (30000/18:33E) contended that this study represented "only a preliminary finding" that is further supported by the results of a more extensive study performed by Haskell Laboratories. The Haskell Laboratories report, submitted by Du Pont during the rebuttal period, is discussed in the following subsection.

(b) Additional Studies Submitted Concerning Skin Sensitization as a Possible Adverse Effect

The following studies of the EBDC's as possible skin sensitizers were submitted by Du Pont.

(1) Haskell Laboratories Report (1969)

A study performed by Haskell Laboratories (1969) and submitted by Du Pont (30000/18:33E) tested the effects of dermal application of the EBDC's to guinea pigs. One test group of guinea pigs was given 10 successive applications of a 20 percent suspension of maneb, a 17-day rest and a challenge dose. The younger animals in this group displayed moderate to severe irritation to the chemical. The older animals showed less irriation but the rate of incidence was not specified. A second test group of guinea pigs was treated with 10-, 25-, and 50-percent suspensions of maneb. Mild to negligible irritation resulted.

In a third test, guinea pigs were given one treatment of 25-percent maneb, a 2-week rest, the first challenge (same suspension), a 27-day rest and a second challenge (same suspension). No irritation occurred after the first challenge, but the second challenge resulted in irritation in eight out of 10 animals.

Agency Finding:

The Agency agrees that the Haskell Laboratories report shows, on the whole, a low degree of sensitization.

(2) Physicians' Reports (1974, 1975)

In addition to the Haskell Laboratories report, Du Pont (30000/18:33E) submitted additional data consisting of physicians' reports of pesticide-related incidences of skin irritation in California (1974, 1975). In 711 cases of skin irritation studied, nine cases involved the EBDC's. Given

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extensive use of the EBDC's in California, Du Pont concluded from these data the EBDC's caused only a small incidence of skin irritation.

Agency Finding:

Although EBDC can cause skin irritation in certain individuals, approximately 1 percent of the skin irritation cases reported in California involved EBDC's. The compounds do not pose a substantial risk to humans; therefore, there is no reason to pursue this issue.

C. Analysis of Exposure

Using information provided by several sources--including the major producers, the Food and Drug Administration (FDA), and the USDA/State/EPA Assessment Team--the Agency has identified human populations exposed to the EBDC's and ETU and examined the type and extent of their exposure. Three avenues of exposure are at issue: dietary (oral), dermal, and respiratory. Given the extensive use of EBDC's on vegetables and fruits, the entire United States population is potentially subject to dietary exposure to ETU. Pesticide applicators who work with EBDC's, farm workers such as weeders and pickers, and bystanders who might be in the vicinity during or immediately after application are also subject to dermal and inhalational exposure.

ETU is a contaminant, degradation product, and metabolite of the EBDC fungicides. ETU has been shown to be oncogenic, teratogenic, and thyrotoxic in animal studies. The EBDC's have also demonstrated oncogenic (maneb and zineb), teratogenic (maneb, zineb, and mancozeb) and thyrotoxic (maneb, zineb, mancozeb, and nabam) effects. However, the oncogenic studies involving maneb and zineb (Balin 1970; Chernov et al. 1969) do not constitute a sufficient basis on which to quantitatively assess oncogenic risk. The NOEL for the thyrotoxic effects of the EBDC's is ten times greater than the NOEL for ETU. Therefore, the Agency conducted the risk assessment based on the exposure to ETU as a result of EBDC usage.

1. Dietary Exposure

a. Additional Dietary Exposure Studies Submitted in Rebuttal

The following residue, market basket, and tabletop studies were submitted in rebuttal:

o Residue study of EBDC-treated fresh tomatoes and processed tomato products (Du Pont, (30000/18:33E).

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- Market basket study of tomatoes and tomato products [Rohm and Haas, 30000/18:132D (Confidential)].

- Market basket study of processed foods (Du Pont, 30000/18:33E).

- Market basket study of fresh and processed foods and potable water (Rohm and Haas, 30000/18:132D).

- Market basket study of a few fresh and processed foods (FMC, Supplement, 30000/18:10D).

- Market basket study of refined sugar and molasses [Alco, 30000/18:27B (Confidential)].

- Two tabletop studies of 100 ready-to-eat meals each [Rohm and Haas, 30000/18:132D and 132G (Confidential); also FMC, 30000/18:10D and 10E].

- The rebuttors claim that the result of these studies should be used instead of tolerance levels of EBDC's to estimate the dietary exposure of ETU.

Agency Finding:

In reviewing the submissions listed above, the Agency found inconsistencies and deficiencies that indicate that some of the studies are of questionable value in determining representative exposure. First, among the market basket studies, the percentage of samples found to contain ETU residue showed a high degree of variability, ranging from 0 percent in the FMC study and less than 0.5 percent in the Rohm and Haas study to 23 percent in the Du Pont study (Reed 1978). This inconsistency might be, in large part, explained in that unlike the FMC and Rohm and Haas studies, the Du Pont study sampled no fresh foods, but processed food items only. As ETU residues would be expected to be higher in the cooked or processed commodities, the pattern found in the rebuttal studies strengthens the Agency's concern about ETU residues in cooked or processed foods. The Agency is concerned in particular that canned spinach was excluded from the market basket studies; all experience in EPA and FDA laboratories has indicated that this is a commodity very likely to contain ETU. Only the market basket study conducted for Rohm and Haas included spinach, and of 60 spinach samples in that study, 30 were raw and 30 frozen. While no ETU was found in the raw spinach, EBDC residues of up to 4.5 ppm were found in the raw spinach, indicating that residues of ETU might be expected in cooked spinach (Reed 1978).

Second, between a market basket study by Rohm and Haas and the studies of samples from EBDC-treated crops (FDA 1978; Phillips 1977), inconsistencies are apparent in the values of the ETU residues found. In the FDA study, all samples of both raw and canned spinach contained ETU at levels ranging from 0.11 to 2.64 ppm in the raw spinach samples and from 0.12 to 1.16 ppm in the canned spinach (FDA, 1978). In the Phillips study (cited in PD 1), ETU residues in frozen spinach samples ranged from 0.02 to 0.76 ppm. In Rohm and Haas' market basket study, an ETU residue of 0.01 ppm was found in only one sample of frozen spinach. The fact that ETU residues in the market basket study never approached the high levels in the samples with known EBDC treatment history heightens concern about the value of the market basket survey in estimating probable dietary exposure.

Use of the limited market basket results in estimating dietary exposure is generally questionable because localized exposure to high residues of EBDC's and ETU could easily have been missed. These localized exposures could result from local use of EBDC-treated animal feedstuffs, local or seasonal weather conditions requiring more frequent fungicide treatment, and possible EBDC residues in water effluents from local industries. This possibility is in fact suggested by the market basket studies themselves, which showed apparent EBDC and ETU residues in food for which no EBDC tolerances have been established, e.g., milk, sugar, bread, butter, and fish (Reed 1978). ETU residues were found at 0.01 ppm in 1 of 30 samples of pasteurized milk, at 0.17 ppm in 1 of 30 samples of refined molasses, and at 1.04 ppm in a sample of crystalline sugar from a beet sugar mill using nabam as a slimicide. The Agency has conducted a milk-monitoring study to determine whether or not EBDC/ETU residues occur in milk from cows fed EBDC-treated sugar beet pulp and molasses. (Residues of ETU in the treated sugar beet pulp and molasses used in the study ranged from 1.5 to 7.8 ppm.) Although no ETU residues were detected in the cow's milk, several problems with the protocol of the study rendered the end results ambiguous (Bradley 1979).

In addition to suggesting possible exposures to EBDC's and ETU not currently covered by tolerances, the market basket studies suggest another potential area of concern: residues in drinking water. Three of 25 samples (12 percent) of potable water from the market basket study (submitted by Rohm and Haas, 30000/18:132D) contained apparent EBDC residues of 0.2 ppm. Of 26 samples of potable water in the same study, a residue of ETU of 0.016 ppm was confirmed initially. However, because the residue was not confirmed a second time, it was ultimately considered undetectable by the respondent.

Given the inconsistencies and limitations summarized above, a worst case estimate based on tolerances and, for purposes of comparison, a lower limit estimate of chronic dietary exposure based on available data including the market basket studies submitted in rebuttal are computed to provide a range of possible risk.

b. Rebuttals Pertaining to Dietary Exposure

Several rebuttals were submitted that criticized the following assumptions used in the Agency's original calculations of dietary exposure:

- That EBDC residues are at tolerance levels.

Although actual residues are almost always less than tolerance levels, tolerances are the possible legal upper limit for residues. These tolerances represent an upper bound on risk.

- That the EBDC's are stoichiometrically converted to ETU, i.e., 100 percent conversion on a mole-to mole basis.

ETU has been found in commercial EBDC formulations at levels that range from 0.02 percent to 2.02 percent (Bontoyan et al. 1972). Furthermore, during storage additional ETU can be formed (Bontoyan and Looker 1973). The EBDC's are converted during cooking by as much as 48.8 percent (Newsome 1976), although the conversion generally ranges from 11 percent to 30 percent (Onley et al., 1977, Watts et al. 1974). In addition, ingested EBDC's are metabolized to ETU in mammalian systems (Seidler et al. 1970). For purposes of a worst-case estimate, the original assumption that the EBDC's are stoichiometrically converted to ETU is retained.

- That 100 percent of the crops involved are treated.

The Agency accepts the commentors' objection to the original assumption that 100 percent of the crops involved are treated with EBDC's. Therefore, when possible, an adjustment has been made to take into account the percentage of individual crops treated with EBDC's, and this adjustment has been factored into both chronic dietary estimates.

Agency Finding:

The respondents contended that these assumed conditions are not observed in the real world and that, therefore, PD 1 overestimated dietary exposure. In response to this overall criticism of the Agency's original estimate of dietary exposure, it is acknowledged that the assumptions proceeded upon do not coincide with real-world conditions. However, such incidental exposure, as the following, indicates that exposure may have been underestimated:

- Possible residues in drinking water from agricultural runoff, or from industrial cooling towers and sugar mills where EBDC's are used (Reed 1978).

- Possible carryover residues in meat, milk, and eggs from the use of treated crops of byproducts (where residues may be concentrated) on feed. Major exposures from feed items where high residues might be expected include apple pomace, tomato pomace, citrus pulp, cannery wastes, milling fractions of cereal grain, vegetable trimmings, and molasses (Reed 1978).

- Residues in sugar and molasses from uses in processing plants (Reed 1978).

- Residues in beer (Gowers and Gordon 1979) also occur.

However, there are many uncertainties surrounding dietary exposure to ETU. Because of the public health issues at stake, current methodologies which permit only crude estimates of human exposure and risk, are designed to avoid understatement of risks. Given the uncertainties associated with dietary exposure to ETU, original estimates may represent not an overstatement but rather an understatement of dietary exposure (Reed 1978).

c. Revised Agency Calculations of Dietary Exposure: Worst Case Estimate

To estimate the degree of risk posed by the use of the EBDC fungicides, the amount of ETU to which a person might be exposed has been calculated. This calculation is presented as a range of possible exposures: an upper limit of dietary exposure (worst case) and a lower limit of dietary exposure (lowest case). The oncogenic and adverse thyroid effects risks are based on chronic exposure, while the teratogenic risk is based on a single exposure. The Agency has based its upper limit of chronic dietary exposure on the following assumptions and principles:

- EBDC residues are assumed to be at tolerance levels.

- EBDC residues are assumed to convert stoichiometrically (mole for mole) to residues of ETU.

- Adjustments have been made to account for the percentage of individual crops treated with EBDC's.

- Commonly used food factors are applicable.

- Possible carryover residues in meat and milk have been taken into account, assuming 0.02 ppm level of detection of ETU.

Table II-6 shows the worst case (upper limit) dietary exposure is 0.00365 mg/kg body weight per day for a 60-kg human. This chronic dietary exposure will be used to calculate the oncogenic and adverse thyroid risks that result from the use of the EBDC's. The acute dietary exposure that was used to estimate teratogenic risk is discussed in Section II.C.i.e.

d. Revised Agency Calculations of Dietary Exposure: Lowest Case Estimate

For purposes of comparison, a lower limit of chronic dietary exposure (lowest case) was estimated using data from the market basket studies and from residue studies when these data were available. In calculating this estimate, the following assumptions and principles were employed (Bradley 1979b):

- The ETU residue for a commodity was calculated as the mean of the positive residues for all samples of that commodity. Raw and processed samples of the commodity were averaged equally.
- Commonly used food factors were applied.
- An adjustment for percentage of crop treated with EBDC's was made. These percentages are shown in Table III-2.
- Samples showing no detectable amounts of ETU or crops for which no data were available were assumed to have amounts of ETU at the limit of detection (0.02 ppm).
- The ETU residues for spinach and tomatoes are the mean of residues from residue studies (FDA 1978; Du Pont 1978).
- Possible carryover residues in meat and milk have been taken into account (Bradley 1979c).

A lowest case estimate of 0.00024 mg/kg body weight per day was calculated for the total dietary exposure of a 60-kg human (Bradley 1979). Table II-7 presents the data for those crops which are under in-depth review.

In addition to direct exposure to ETU, the EBDC residue left on food can be metabolically converted to ETU. The following assumptions were made to calculate the amount of ETU which can result from indirect exposure (Bradley 1979b):

- The EBDC residue for a commodity was calculated as the weighted mean residues from the studies submitted in rebuttal and the mean residue of the FDA study (Bradley 1979b).

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Table II-6. Worst-Case Estimates of ETU Dietary Exposure for U.S. Population

Crop	Exposure (mg/kg bw/day)
Apples	5.97×10^{-4}
Bananas	6.83×10^{-5}
Beans, Lima	1.33×10^{-5}
Beans, Snap	3.77×10^{-4}
Cabbage	1.33×10^{-4}
Celery	6.00×10^{-5}
Citrus	1.23×10^{-4}
Corn, Sweet	2.58×10^{-4}
Cucurbits	3.93×10^{-4}
Grapes	8.33×10^{-6}
Lettuce	3.67×10^{-4}
Mushrooms	1.17×10^{-5}
Onions	1.40×10^{-4}
Peanuts	3.33×10^{-5}
Peppers, Green	1.83×10^{-5}
Plums/Prunes	1.67×10^{-6}
Potatoes	2.77×10^{-4}
Spinach	2.83×10^{-5}
Tomatoes	3.32×10^{-4}
Small Grains	9.33×10^{-5}
Other Fruit	7.83×10^{-5}
Milk	1.14×10^{-4}
Meat	6.93×10^{-5}
Total	3.65×10^{-3}

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Table II-7. Lowest-Case Estimates of ETU Dietary Exposure for U.S. Population

Use	Residue ppm	% Diet	mg/kg bw/day	% Crop Treated	Adjusted mg/kg bw/day
Apples	0.02	2.53	$1.27\text{x}10^{-5}$	35	$4.43\text{x}10^{-6}$
Bananas	0.02	1.42	$7.10\text{x}10^{-6}$	100	$7.10\text{x}20^{-6}$
Beans, Lima	0.02	0.19	$9.50\text{x}10^{-7}$	7.3	$6.94\text{x}10^{-8}$
Beans, Snap	0.02	0.98	$4.90\text{x}10^{-6}$	40	$1.96\text{x}10^{-6}$
Cabbage	0.02	0.74	$3.70\text{x}10^{-5}$	18.6	$6.88\text{x}10^{-7}$
Celery	0.02	0.29	$1.45\text{x}10^{-6}$	43.1	$6.25\text{x}10^{-7}$
Citrus	0.02	3.81	$1.91\text{x}10^{-5}$	5	$9.53\text{x}10^{-7}$
Corn, Sweet	0.02	2.25	$1.13\text{x}10^{-5}$	37.6	$4.23\text{x}10^{-6}$
Cucurbits	0.02	2.84	$1.42\text{x}10^{-5}$	35	$4.97\text{x}10^{-6}$
Grapes	0.02	0.45	$2.25\text{x}10^{-6}$	2.5	$5.63\text{x}10^{-8}$
Lettuce	0.02	1.31	$6.55\text{x}10^{-6}$	29.1	$1.91\text{x}10^{-6}$
Mushrooms	0.02	0.03	$1.50\text{x}10^{-7}$	63	$9.45\text{x}10^{-8}$
Onions	0.02	0.83	$4.15\text{x}10^{-6}$	25	$1.04\text{x}10^{-6}$
Peanuts	0.02	0.36	$1.80\text{x}10^{-6}$	14.4	$2.59\text{x}10^{-7}$
Peppers, Green	0.02	0.12	$6.00\text{x}10^{-7}$	22.2	$1.33\text{x}10^{-7}$
Plums/Prunes	0.02	0.13	$6.50\text{x}10^{-7}$	2	$1.30\text{x}10^{-8}$
Potatoes	0.02	5.43	$2.72\text{x}10^{-5}$	53	$1.44\text{x}10^{-5}$
Spinach	0.73	0.05	$9.13\text{x}10^{-5}$	59	$5.38\text{x}10^{-6}$
Tomatoes	0.03	2.87	$2.15\text{x}10^{-5}$	30	$6.46\text{x}10^{-6}$
Small Grains	0.02	11.86	$5.93\text{x}10^{-5}$	1.8	$1.07\text{x}10^{-6}$
Other Fruit	0.02	1.88	$9.40\text{x}10^{-6}$	4.8	$4.51\text{x}10^{-7}$
Milk	0.02	22.75	$1.14\text{x}10^{-4}$	N.A.	$1.14\text{x}10^{-4}$
Meat	0.02	13.85	$6.93\text{x}10^{-5}$	N.A.	$6.93\text{x}10^{-5}$
Total			$4.01\text{x}10^{-4}$		$2.39\text{x}10^{-4}$

Source: Bradley (1979c)

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- Generally-used food factors were applied.

- Because these commodities, except spinach, were sampled at random, no adjustment for percent of crop treated was made.

- Crops for which no analyses were performed were assumed to have amounts of EBDC at the limit of detection (0.2 ppm).

- An adjustment for percentage of crop treated with EBDC's was made for spinach and for crops having no residue data available.

- Table II-8 presents data for those crops that are under in-depth review. An additional 0.00010 mg of ETU per kg body weight per day could result from the metabolic conversion (18%) of 0.00056 mg of EBDC per kg body weight per day. A person, therefore, could be exposed to a total of 0.00034 mg of ETU per kg body weight per day.

e. Revised Agency Calculation of Dietary Exposure: Acute-Case Estimates

Because teratogenic risk can result from a single exposure on the critical days of gestation, the Agency has calculated acute dietary exposure based on the following principles and assumptions:

- EBDC residues are assumed to be at tolerance levels.

- For the upper-limit acute dietary exposure, EBDC residues are assumed to convert stoichiometrically (mole for mole) to ETU.

- For the lower-limit acute dietary exposure, 18 percent of EBDC residues are assumed to convert to ETU (Johnson 1980).

- The weight of a single service has been calculated based on data reported in Family Food Buying, Home Economic Research Report No. 37, Agricultural Research Service, Revised August 1977 (Johnson 1980).

- Tables II-9 and II-10 present the estimates of acute dietary exposure that will be used to estimate teratogenic risks.

2. Applicator Exposure

Two studies of applicator exposure (dermal and respiratory exposure) to EBDC's and ETU, both of which were

Table II-8. EBDC Dietary Exposure for U.S. Population

Use	Residue ppm	% Diet	mg/kg bw/day	% Crop Treated	Adjusted mg/kg bw/day
Apples	0.031	2.53	1.96×10^{-5}		1.96×10^{-5}
Bananas	0.2	1.42	7.10×10^{-5}	100.0*	7.10×10^{-5}
Beans, Lima	0.067	0.19	3.18×10^{-6}		3.18×10^{-6}
Beans, Snap	0.048	0.98	1.18×10^{-5}		1.18×10^{-5}
Cabbage	0.088	0.74	1.63×10^{-5}		1.63×10^{-5}
Celery	0.040	0.29	2.90×10^{-6}		2.90×10^{-6}
Citrus	0.005	3.81	4.76×10^{-6}		4.76×10^{-6}
Corn, Sweet	0.016	2.25	9.00×10^{-6}		9.00×10^{-6}
Cucurbits	0.022	2.84	1.56×10^{-5}		1.56×10^{-5}
Grapes	0.2	0.49	2.45×10^{-5}	2.5*	6.13×10^{-7}
Lettuce	0.2	1.31	6.55×10^{-5}	29.1*	1.91×10^{-5}
Mushrooms	0.2	0.03	1.50×10^{-6}	63.0*	9.45×10^{-7}
Onions	0.310	0.83	6.43×10^{-5}		6.43×10^{-5}
Peanuts	0.2	0.36	1.80×10^{-5}	14.4*	2.59×10^{-6}
Peppers, Green	0.2	0.12	6.00×10^{-6}	22.2*	1.33×10^{-6}
Plums	0.2	0.13	6.50×10^{-6}	2.0*	1.30×10^{-7}
Potatoes	0.045	5.43	6.11×10^{-5}		6.11×10^{-5}
Spinach**	19.1	0.05	2.39×10^{-4}	59.0**	1.41×10^{-4}
Tomatoes	0.005	2.87	3.59×10^{-6}		3.59×10^{-6}
Small Grains	0.02	11.86	5.93×10^{-5}		5.93×10^{-5}
Other Fruit	0.118	1.88	5.55×10^{-5}		5.55×10^{-5}
Total			7.59×10^{-4}		5.64×10^{-4}

Source: Bradley (1979b)

* Where no data are available, method sensitivity (0.2 ppm) is used and adjusted for percent of crop treated.

Table II-9. Upper-Limit "Single-Service Estimate" of Dietary Exposure

Food	Serving Size (kg)	ETU (mg/serving)	Exposure (mg/kg/day)
Apples	0.212	0.725	0.0121
Bananas	0.136	0.026	0.0004
Beans, Lima	0.072	0.274	0.0046
Beans, Snap	0.055	0.209	0.0035
Cabbage	0.090	0.342	0.0057
Celery	0.160	0.304	0.0051
Citrus			
(Grapefruit)	0.121	0.322	0.0054
(Oranges)	0.245	0.652	0.0109
Corn, Sweet	0.080	0.152	0.0025
Cucurbits			
(Cucumbers)	0.144	0.219	0.0036
(Squash)	0.222	0.590	0.0098
Grapes	0.081	0.215	0.0036
(Raisins)	0.142	1.511	0.0252
Lettuce	0.057	0.217	0.0036
Mushrooms	0.095	0.253	0.0042
Onions	0.171	0.455	0.0076
Peanuts	0.152	0.404	0.0067
Peppers, Green	0.100	0.266	0.0044
Plums/Prunes	0.070	0.186	0.0031
Potatoes	0.169	0.064	0.0011
Spinach	0.055	0.209	0.0035
Tomatoes	0.181	0.275	0.0056

Source: Johnson (1980)

Table II-10. Lower-Limit "Single-Service Estimate" of Dietary Exposure

Food	Serving Size (kg)	ETU (mg/serving)	ETU (mg/kg bw/serving)
Apples	0.212	0.343	0.0057
Bananas	0.136	0.012	0.0002
Beans, Lima	0.072	0.130	0.0022
Beans, Snap	0.055	0.099	0.0016
Cabbage	0.090	0.162	0.0027
Celery	0.160	0.144	0.0024
Citrus			
(Grapefruit)	0.121	0.152	0.0025
(Oranges)	0.245	0.309	0.0051
Corn, Sweet	0.080	0.072	0.0012
Cucurbits			
(Cucumbers)	0.144	0.103	0.0017
(Squash)	0.222	0.280	0.0047
Grapes	0.081	0.102	0.0017
(Raisins)	1.142	0.716	0.0119
Lettuce	0.057	0.103	0.0017
Mushrooms	0.095	0.120	0.0020
Onions	0.171	0.215	0.0036
Peanuts	0.152	0.192	0.0032
Peppers, Green	0.100	0.126	0.0021
Plums/Prunes	0.070	0.088	0.0015
Potatoes	0.169	0.300	0.0005
Spinach	0.055	0.099	0.0016
Tomatoes	0.181	0.130	0.0022

Source: Johnson (1980)

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submitted in rebuttal, were used to estimate applicator exposure. Rohm and Haas supplied data on both dermal and respiratory exposure to mancozeb and ETU for mixer/loaders and applicators during actual airblast, ground, and aerial spray applications. Mallinckrodt supplied data on respiratory exposure, but not dermal exposure, to mancozeb and ETU during boom spray application to golf turf.

The Rohm and Haas study is less than comprehensive because only two exposure situations were sampled for the airblast use and only one instance each for ground spray and aerial application. Nevertheless, the Rohm and Haas study is preferable to an extrapolation approach because it better represents actual EBDC use than do other studies. Extrapolation from other studies would not satisfactorily measure ETU exposure.

The Rohm and Haas study (1978) used a colorimetric analytical method to measure CS_2 evolution from Dithane M-45 (mancozeb) at a level of detection of about 7.5μg/sampling pad. A GC-flame photometric method for determining the s-butyl derivative of ETU at a level of detection of about 0.1 g/sampling pad was also used in the study.

The Dithane CS_2 analysis is not specific for EBDC, but is more likely to result in false positives than false negatives. Recoveries ranged from 87 percent to 103 percent for pad samplings (100 percent average). The ETU derivation method may result in formation of small quantities of ETU from EBDC residues during analysis itself. Recoveries were more variable, ranging from 31 percent to 137 percent (70 percent average).

All test samples were corrected for recovery. However, samples were corrected for overall average recoveries, not for individual spiked recoveries pertaining to each study.

No confirmatory analysis by mass spectrometer (MS) or infrared (IR) was undertaken, so the final results must be considered tentative.

The exposure study measured dermal and inhalational exposure to Dithane M-45 (mancozeb). Application rates were 4.8 pounds of active ingredient per acre for airblast, 2.4 pounds of active ingredient per acre for ground spray and 2.4 pounds active ingredient per acre for aerial application. The airblast sprayer was operated at 300 PSI with only one side spraying at a time. The ground sprayer was operated at 40 PSI and aircraft nozzles were operated at 175 [illegible]. Dermal exposure was monitored on gauze pads and cotton gloves; respiratory exposure was monitored by an adapted respirator fitted with cellulose or gauze filters.

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The ETU values reported by Rohm and Haas for Dithane M-45 application may underestimate the ETU exposure resulting from other EBDC products. Mancozeb has been reported to contain lower concentrations of ETU than maneb or zineb. Averages of maneb/zineb samples analyzed for ETU content by Bontoyan et al. (1972) and by Bontoyan and Looker (1973) yielded 0.7 percent ETU content. In contrast, averages of mancozeb samples analyzed by the same researchers yielded 0.1 percent ETU content. To extrapolate the current Rohm and Haas monitoring study to other EBDC products, the Agency applied a correction factor of 7 to the Rohm and Haas ETU results. Table II-11 presents the exposure data on an hourly basis by type of application activity when the following assumptions are made, based on the Rohm and Haas study:

- The applicator wears a short sleeve, open neck shirt, long pants, and no gloves or respirator.
- 10 % dermal absorption occurs.
- 100 % respiratory absorption occurs.
- EBDC values are based on exposure to mancozeb.
- A correction factor of 7 was applied to ETU results (see discussion above) except for aerial mixer/loaders.
- A stoichiometric conversion (mole for mole) of EBDC's to ETU was made for aerial mixer/loaders.
- Airblast application was made at a rate of 4.8 pounds of active ingredient per acre.
- Ground spray and aerial applications were made at rate of 2.4 pounds of active ingredient per acre.
- Exposure rates may be extrapolated on the basis of application rate ratios (see discussion of Small et al. below).

Small et al. (1977) performed an inhalation exposure monitoring study during spray operations on golf turf. One portion of the study involved application of 7.7 pounds active ingredient mancozeb per acre with a tractor-drawn boom sprayer. Applicator inhalation exposure amounted to 0.06 mg of mancozeb per hour. This value is three times greater than the value of the ground spray applicator exposure measured by Rohm and Haas (1978). Since the application rate was also three times greater than that used in the Rohm and Haas study, the results indicate that applicator inhalation exposure may be extrapolated on the basis of application rate ratios. The

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Table II-11. Hourly Exposure to EBDC and ETU

Exposure Activity	DERMAL CONTACT (mg/hr)		INHALATION EXPOSURE (mg/hr)		TOTAL EXPOSURE[3] (mg/hr)	
	EBDC	ETU[2]	EBDC	ETU[2]	EBDC	ETU[2]
Airblast Application[1]	6.9	1.4	0.03	0.007	0.72	0.15
Airblast Mixing/Loading[1]	33.7	9.2	0.5	0.042	3.87	0.96
Ground Spray Application	2.8	0.3	0.2	-	0.3	0.03
Ground Spray Mixing/Loading	179.3	4.2	0.66	-	18.59	0.42
Aerial Application	12.3	3.7	0.08	0.007	1.31	0.38
Aerial Mixer/ Loader	218.1	82.9[4]	0.16	0.028	21.97	13.1

Sour[illegible]ohm and Haas study

ALL EBDC VALUES BASED ON EXPOSURE TO MANCOZEB

[1] Average of two values.

[2] Corrected for ETU content (7x), see text.

[3] Assuming 10 percent dermal penetration and 100 percent inhalation penetration.

[4] Assuming stoichiometric conversion of EBDC's to ETU.

ratios between dermal exposure and respiratory exposure are likely to be constant for each specific exposure situation; therefore, dermal exposure data can also be extrapolated on the basis of application rates. The inhalation exposure for mixer/loaders in the Small et al. (1977) study was 0.28 mg of mancozeb per hour.

Daily, seasonal, and annual exposure to ETU were used to calculate risks (Mittelman 1979). Because teratogenic effects can occur from even a single exposure, the exposure experienced during each application has been used to estimate teratogenic risk. Because the NOEL for adverse thyroid effects was established using subchronic testing, the total exposure experienced during a season divided by the number of days of the season has been used to estimate the adverse thyroid effect. Because the oncogenic risk is based on lifetime exposure, the total annual exposure divided by 365 days has been used to calculate oncogenic risk. The Agency has not included oral exposure when determining applicator exposure. A brief discussion of the additional oral exposure to applicators is presented in the discussions on risk.

D. Risk Assessment

Following is the Agency's assessment of the potential risks of EBDC's based on the available toxicology data and the estimated exposure to humans and wildlife.

1. Aquatic Toxicity

The use of mancozeb on wild rice met the acute RPAR trigger for aquatic organisms when it was shown that mancozeb residues in water would exceed one half the acute LC_{50} for aquatic organisms likely to be exposed.

After analyzing the use patterns, practices, and the extent to which mancozeb is used, however, the Agency believes that the potential for both national and local adverse effects is low.

The extent of mancozeb use on wild rice is limited. Only an estimated 15,000 acres of commercial wild rice paddies in Minnesota are treated with mancozeb annually. No wild rice grown in lakes or other non-commercial areas is treated. Thus, it can be concluded with reasonable certainty that, on a national basis, adverse effects to aquatic organisms are not likely.

While there is some potential for adverse effects on local fish populations, certain agricultural practices associated with growing wild rice also indicate that exposure will be kept to a minimum. Mancozeb is applied up to four times per season at intervals of approximately 10 days. Generally, the fields (paddies) are flooded as early as possible in the growing season and are then allowed to drain (percolate and evaporate down by final application and harvest, a period from the end of July to the beginning of August). Usually the first two applications are made when water is standing and the final two when most or all of the water is gone. At the very worst, a heavy rainfall (4-5 inches over an unspecified period of time) would require some draw down to remove the water before harvest.

The Agency concludes that because mancozeb use is limited to commercially grown wild rice and because current use practices prevent deliberate exposure to nontarget organisms, no unreasonable adverse effects are expected as long as appropriate label changes are adopted as discussed in Chapter V.

2. Oncogenicity

When the Agency judges a chemical to be a potential human carcinogen, it estimates the risk to exposed populations according to the principles and procedures set forth in the Agency's Interim Guidelines for Carcinogen Risk Assessment (41 FR 21402, May 25, 1976). These guidelines state that a substance will be considered a "presumptive cancer risk when it causes a statistically significant excess incidence of benign or malignant tumors in humans or animals."

For the EBDC's, enough evidence existed to trigger a presumption of oncogenicity and to conduct a risk and benefit assessment.

According to the Interim Guidelines, a risk assessment should provide a judgment concerning the weight of evidence that an agent is a potential human carcinogen. If the agent is judged to be a potential carcinogen, estimates should be made of its possible impact on public health.

The weight of evidence--the quality of the data and the kinds of tumorigenic responses induced by the EBDC's and ETU in animals--was discussed in the rebuttal section of this document (II.A.2.) It was concluded that the presumption of oncogenicity was not rebutted, since statistically significant incidences of several types of tumors were observed in different animals for maneb, zineb and ETU (see Table II-1). The Agency responded to comments that the quality of the EBDC studies was deficient, that the mouse is an inappropriate test animal for judging oncogenicity, and that the observed thyroid and liver tumors might have been induced indirectly rather than directly.

Further, The Agency believes that a pituitary thyroid feedback mechanism may be involved in the occurrence of thyroid carcinomias from the admininistration of ETU to rats. However, this thesis has not been tested by chronic testing involving coadministration of thyroid hormone and test chemical to assay carcinogenicity. Additional short term mammalian in vitro testing for each of the EBDC's will be required to exclude genotoxicity. Mammalian cell transformation assays will also be required for ETU and each of the EBCD's to elucidate the mechanism of action for oncogenesis.

The Agency also believes that the inhibitory effect of several EBDC's, EBIS, a metabolite of EBDC's and other thiourea analogues on mixed function oxidase enzymes in the liver must be considered in assessing the significance of the mouse liver tumors. Several of these thiourea analogues, some of which are metabolites of ETU, are known to induce hepatic necrosis (see, for example Jordan and Neal). In order to elucidate the mechanism of liver oncogenesis, the Agency needs data for EBDC's and ETU and additional mutagenicity data for each of the EBDC's, as well as detailed metabolic studies to supplement the results.

These issues are significant because they add uncertainty to the selection of an appropriate risk assessment model. Until additional evidence is provided to clarify the mechanism of action of the EBDC's and ETU, this issue will remain an uncertainty to be factored into the Agency's regulatory decision on EBDC's.

Despite the uncertainty over the mode of action of ETU, the Agency assumes that any agent that causes tumors in animals may have the potential to induce them in humans. To conduct a quantitative risk assessment, the Agency used the following methods and assumptions:

- Animal data. Since the EBDC studies were deficient for quantitative risk assessment, a study on ETU was selected. The study with the most sensitive oncogenic response was observed in mice exposed to ETU (the Innes study) and was used as the basis for the quantitative estimation of risk.

- Risk extrapolation model. The one-hit model (a linear nonthreshold model) was used to calculate the mathematical probability that an individual will develop a tumor due to exposure to ETU in that person's lifetime. The linear model is used to give an estimate of a plausible upper-bound of lifetime cancer risk, recognizing that uncertainties in the extrapolation process may result in a lower-bound of zero risk. In view of the issues discussed above about mouse liver and rat thyroid oncogenesis for these chemicals, and the inconclusive nature of the presently available evidence for mutagenicity, the upper bound of risk is regarded as tentative until further studies are performed.

- **Dietary Exposure**. Risks were calculated for both the worst-case (based on tolerance level and a 38 percent conversion rate of EBDC to ETU) and lowest-case (based on market basket data or on level of detection) estimates of dietary exposure. The risks appear in Table II-12. A lifetime exposure of 70 years was assumed. Uncertainties concerning the dietary exposure estimates were discussed in Section II.C.1.

- **Applicator Exposure**. Estimates of applicator exposure were calculated using the average and the maximum number of applications per season. 18 percent conversion of EBDC to ETU was assumed. The risk estimates appear in Tables II-13 through II-15.

3. Teratogenicity

The teratogenic risk has been evaluated by comparing the NOEL in animal studies with the highest calculated daily acute exposure for each use for human populations. The resulting ratios are referred to as margins of safety (MOS) and represent, at best, a crude measure of risk to the various exposed populations (Sandusky 1978). The Agency used the NOEL of 5 mg/kg per body weight per day for ETU (Khera 1973) for calculating margins of safety for EBDC's.

a. General Population Risk

The Agency has calculated an upper limit and lower limit of exposure to ETU based on EBDC's being present on crops at tolerance levels. The upper limit results when 100 percent of the EBDC's in or on a food crop is converted to ETU. The lower limit results when EBDC's are metabolically converted to ETU. Metabolism studies have shown that 100 milligrams of EBDC are converted metabolically to approximately 18 milligrams of ETU (Lyman and Locoste 1975).

The NOEL found in the Khera study is sufficiently greater than the anticipated exposure to ETU from food intake alone to conclude that the current use of EBDC on food crops would pose no unreasonable teratogenic risk to humans. Table II-16 presents the MOS for selected food crops.

b. Applicator Risk

Smaller subpopulations engaged in the application of EBDC's could experience greater exposure and concurrent risk than that identified for the general population.

Estimates of exposure to these subpopulations are identified in Section II.C, and the MOS for each subgroup is presented in Tables II-18, II-19, and II-20.

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Table II-12. Dietary Risk Assessment -- Oncogenicity

Source of Exposure	Lifetime Probability Worst-case Estimate	Lifetime Probability Lowest-case Estimate
Apples	8.5×10^{-5}	1.1×10^{-6}
Bananas	1.0×10^{-5}	2.8×10^{-6}
Beans, Lima	1.9×10^{-6}	9.2×10^{-8}
Beans, Snap	5.4×10^{-6}	5.8×10^{-7}
Cabbage	1.9×10^{-5}	5.2×10^{-7}
Celery	8.6×10^{-6}	1.6×10^{-7}
Citrus	1.8×10^{-5}	2.6×10^{-7}
Corn, Sweet	3.7×10^{-5}	8.4×10^{-7}
Cucurbits	5.6×10^{-5}	1.1×10^{-6}
Grapes	1.2×10^{-6}	2.3×10^{-8}
Lettuce	5.2×10^{-5}	7.6×10^{-7}
Mushrooms	1.7×10^{-6}	3.8×10^{-8}
Onions	2.0×10^{-5}	1.8×10^{-6}
Peanuts	4.8×10^{-6}	1.0×10^{-7}
Peppers, Green	2.6×10^{-6}	5.3×10^{-8}
Plums/Prunes	2.4×10^{-7}	5.2×10^{-9}
Potatoes	4.0×10^{-5}	3.6×10^{-6}
Spinach	4.0×10^{-6}	4.4×10^{-6}
Tomatoes	4.7×10^{-5}	1.0×10^{-6}
Small Grains	1.3×10^{-5}	1.7×10^{-6}
Other Fruit	1.1×10^{-5}	1.5×10^{-6}
Milk	1.6×10^{-5}	1.6×10^{-5}
Meat	9.9×10^{-6}	9.9×10^{-6}
Total	4.9×10^{-4}	4.8×10^{-5}

Source: Anderson, 1979

Table II-13. Row Boom Applicator Risk Assessment -- Oncogenicity

Source of Exposure	Lifetime Probability
Cabbage	(2.3-4.0) x 10^{-5}
Cantaloupe	(3.4-7.1) x 10^{-5}
Celery	(2.4-7.1) x 10^{-4}
Cucumber	(1.5-2.1) x 10^{-4}
Lettuce	3.4 x 10^{-4}
Lima Beans	1.3 x 10^{-4}
Onions	(0.5-1.3) x 10^{-4}
Peppers	(2.4-2.6) x 10^{-5}
Potatoes	(3.9-9.4) x 10^{-5}
Snap Beans	(9.0-9.4) x 10^{-5}
Spinach	(0.9-1.0) x 10^{-4}
Sweet Corn	(1.3-2.1) x 10^{-4}
Tomatoes	(1.9-5.0) x 10^{-5}
Watermelon	(1.9-2.1) x 10^{-5}
Home & Garden (spray)	(2.1-3.1) x 10^{-5}
Home & Garden (dust)	(2.6-3.9) x 10^{-5}
Chrysanthemums	2.0 x 10^{-4}
Gladiolas	(4.1-8.1) x 10^{-5}
Foliage	-----
Conifers	(4.7-5.7) x 10^{-4}
X-Trees	(3.9-4.6) x 10^{-4}
Turf	(0.8-1.6) x 10^{-4}
Grass Seed	9.2 x 10^{-5}

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Table II-14. Airblast Applicator Risk Assessment -- Oncogenicity

Source of Exposure	Applicator/Mixer/Loader Lifetime Probability	Mixer/Loader Lifetime Probability
Apples	(0.8-1.4) x 10^{-4}	(4.7-7.9) x 10^{-5}
Peaches	(5.4-9.2) x 10^{-5}	(2.3-4.1) x 10^{-5}
Pears	(4.7-7.4) x 10^{-5}	(2.0-3.1) x 10^{-5}
Citrus		------
Potatoes	(3.9-8.2) x 10^{-5}	(2.3-5.1) x 10^{-5}
Nectarine	(5.1-8.7) x 10^{-5}	(2.0-3.6) x 10^{-5}
Grapes	(2.0-2.4) x 10^{-5}	(1.2-1.6) x 10^{-5}
Wild Rice	1.2 x 10^{-4}	9.0 x 10^{-5}

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Table II-15. Aerial Applicator Risk Assessment -- Oncogenicity

Source of Exposure	Pilots Lifetime Probability	Mixer/Loader Lifetime Probability
Apples	$(0.8-4.7) \times 10^{-5}$	$(0.7-4.3) \times 10^{-4}$
Cabbage	$(5.1-8.6) \times 10^{-5}$	$(1.3-2.1) \times 10^{-3}$
Celery	$(0.5-1.6) \times 10^{-4}$	$(2.0-5.7) \times 10^{-3}$
Cucumber	$(7.7-9.1) \times 10^{-5}$	$(2.0-2.3) \times 10^{-3}$
Lettuce	7.6×10^{-5}	1.3×10^{-3}
Peppers	6.4×10^{-5}	1.1x x 10-3
Potatoes	$(1.6-3.6) \times 10^{-4}$	$(3.6-8.6) \times 10^{-3}$
Snap Beans	1.9×10^{-5}	2.6×10^{-3}
Sweet Corn	$(2.7-4.4) \times 10^{-4}$	$(0.6-1.1) \times 10^{-2}$
Tomatoes	$(4.1-1.2) \times 10^{-4}$	$(0.5-2.6) \times 10^{-3}$
Watermelon	$(1.6-1.7) \times 10^{-4}$	$(2.6-3.0) \times 10^{-3}$
Barley & Wheat	2.1×10^{-5}	4.3×10^{-4}
Wild Rice	2.1×10^{-5}	4.6×10^{-4}
Peanuts	3.1×10^{-5}	8.6×10^{-4}
Sugar Beets	$(1.1-2.1) \times 10^{-5}$	$(1.5-2.9) \times 10^{-4}$
Cotton	1.6×10^{-5}	2.1×10^{-4}
Dry Beans	2.1×10^{-5}	4.3×10^{-4}

Table II-16. Dietary Risk Assessment -- Teratogenicity

Food	Exposure mg/kg/day	MOS
Apples	0.0057 - 0.0121	>900 - 400
Bananas	0.0002 - 0.0004	>1000
Beans, Lima	0.0022 - 0.0046	>1000
Beans, Snap	0.0016 - 0.0035	>1000
Cabbage	0.0027 - 0.0057	>1000 - 900
Celery	0.0024 - 0.0051	>1000
Citrus		
Grapefruit	0.0025 - 0.0053	>1000 - 900
Oranges	0.0051 - 0.0109	>1000 - 500
Corn, Sweet	0.0012 - 0.0025	>1000
Cucurbits		
Cucumbers	0.0017 - 0.0036	>1000
Squash	0.0046 - 0.0098	>1000 - 500
Grapes	0.0017 - 0.0036	>1000
Raisins	0.0119 - 0.0252	400 - 200
Lettuce	0.0017 - 0.0036	>1000
Mushrooms	0.0020 - 0.0042	>1000
Onions	0.0036 - 0.0075	>1000 - 700
Peanuts	0.0032 - 0.0067	>1000
Peppers, Green	0.0021 - 0.0044	>1000
Plums/Prunes	0.0015 - 0.0031	>1000
Potatoes	0.0005 - 0.0011	>1000
Spinach	0.0016 - 0.0035	>1000
Tomatoes	0.0022 - 0.0056	>1000 - 900

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Table II-17. Dietary Thyroid Risk to the General Public

Food	Exposure mg/kg/day	MOS
Apples	6×10^{-7} to 4×10^{-6}	400 - >1000
Bananas	7×10^{-5} to 7×10^{-6}	>1000
Beans, Lima	1×10^{-5} to 7×10^{-8}	>1000
Beans, Snap	4×10^{-4} to 2×10^{-6}	600 - >1000
Cabbage	1×10^{-4} to 7×10^{-7}	>1000
Celery	6×10^{-5} to 6×10^{-7}	>1000
Citrus	1×10^{-4} to 1×10^{-6}	>1000
Corn, Sweet	2×10^{-4} to 4×10^{-6}	>1000
Cucurbits	4×10^{-4} to 5×10^{-6}	600 - >1000
Grapes	8×10^{-6} to 6×10^{-8}	>1000
Lettuce	4×10^{-4} to 2×10^{-6}	600 - >1000
Mushrooms	1×10^{-5} to 9×10^{-8}	>1000
Onions	1×10^{-4} to 1×10^{-6}	>1000
Peanuts	3×10^{-5} to 2×10^{-7}	>1000
Peppers, Green	2×10^{-5} to 1×10^{-7}	>1000
Plums/Prunes	1×10^{-6} to 1×10^{-8}	>1000
Potatoes	3×10^{-4} to 1×10^{-5}	800 - >1000
Spinach	3×10^{-5} to 5×10^{-6}	>1000
Tomatoes	3×10^{-4} to 6×10^{-6}	800 - >1000
Small Grains	9×10^{-5} to 1×10^{-6}	>1000
Other Fruit	8×10^{-5} to 4×10^{-7}	>1000
Milk	1×10^{-4}	>1000
Meat	7×10^{-5}	>1000
Total	4×10^{-3} to 2×10^{-4}	60 - >1000

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Table II-18. Aerial Applicator Risk Assessment -- Teratogenicity

Use Site	Pilots MOS Teratogenicity	Mixer/Loader MOS Teratogenicity
Apples	200-300	25-50
Cabbage	200-300	<10
Celery	200-300	<10
Cucumber	200-300	<10
Lettuce	100-150	<10
Peppers	500	<10
Potatoes	100	<10
Snap Beans	100-150	<10
Sweet Corn	100-150	<10
Tomatoes	600	10-25
Watermelon	100-150	<10
Barley & Wheat	300-500	10-25
Wild Rice	600	10-25
Peanuets	600	10-25
Sugar Beets	700	10-25
Cotton	700	10-25
Dry Beans	100	<10

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Table II-19. Airblast Risk Assessment -- Teratogenicity and Thyroid Effects

Use Site	Applicator/Mixer/Loader Teratogenicity MOS	Applicator/Mixer/Loader Thyroid Effect MOS	Mixer/Loader Teratogenicity MOS	Mixer/Loader Thyroid Effects MOS
Apples	100-200	100-200	200-300	150-200
Peaches	200	75-100	400-500	100-150
Pears	150-200	100-200	500	150-250
Citrus	50	---	100-150	---
Potatoes	200-300	100-200	500	350-400
Nectarine	200-300	10-50	500	100-200
Grapes	1000	800	>1000	450-600
Wild Rice	10-50	10-25	50-100	25-50
Plums/Prunes	>1000		>1000	>1000

Table II-20. Row Boom Applicator Risk Assessment -- Teratogenicity and Thyroid Effects

Use Site	Teratogenicity Mos	Thyroid Effects Mos
Cabbage	>1000	700-800
Cantaloupe	>1000	>1000
Celery	400	100-200
Cucumber	600-700	300-400
Lettuce	100	50-75
Lima Beans	400-500	100-200
Onions	800-900	300-400
Peppers	>1000	>1000
Potatoes	>1000	>1000
Snap Beans	800-900	300-400
Spinach	600-700	300
Sweet Corn	1000	400-500
Tomatoes	500-600	300
Watermelon	>1000	>1000
Home & Garden (spray)	>1000	250-350
Home & Garden (dust)	500	200-300
Chrysanthemums	250-300	75-100
Gladiolas	>1000	350-650
Foliage	250-300	
Conifers	50	50-100
X-Trees	50	75-100
Turf	500	200-300
Grass Seed	75-100	25-50

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4. Thyroid Toxicity

The thyroid risk has been evaluated by comparing the NOEL in animal studies with the seasonal exposure for populations at risk. The resulting ratios are the margins of safety.

The Agency considered the NOEL for thyroid effects to be 0.240 mg/kg body weight per day (Freudenthal 1977). Margins of safety are given in Tables II-19, II-20, and II-21 for applicators. Table II-17 shows margins of safety for the United States population.

5. Mutagenicity

The Agency has published Proposed Guidelines for Mutagenicity Risk Assessment (45 FR 74984; November 13, 1980). These guidelines state that "The judgment as to whether a chemical substance is likely to be a potential human mutagen will be based on a weight-of-evidence approach that involves and considers the quality and adequacy of all the available data." The Agency must determine whether there is strong, substantial, or only suggestive evidence that a particular chemical may be potentially mutagenic to humans.

a. Mutagenicity of the EBDC's

A large number of mutagenicity studies have been conducted on the EBDC's (see Tables II-5 (b) and (d)). The majority of these studies, however, are not acceptable, according to current Agency criteria, due to inadequate protocols, insufficient reporting, unsubstantiated results etc. Further, when considered separately, none of these fungicides has been adequately tested with respect to several genetic end-points of concern (gene mutation, cytogenetic damage, DNA damage/repair). Thus, the data are inconclusive. Only a few tentative presumptions can be drawn: (1) That maneb and zineb may be weakly mutagenic in some microbial assays (notably recombination tests in fungid, and (2) that there is only suggestive evidence of interference with repair process (maneb, zineb) and chromosome integrity (mancozeb) in mammalian systems.

The Agency has concluded that while the results of mutagenicity testing of the EBDC's have not demonstrated firm mutagenic potential, the quality of the data base also does not permit a determination of the absence of mutagenic activity. Additional testing is required, as described in Section V.D.4., to evaluate adequately the mutagenicity of each of the six EBDC chemicals.

b. Mutagenicity of ETU

As summarized in Section II.B.2, Tables II-5, (a) and (c), ETU has been extensively tested in a wide variety of

Table II-21. Aerial Applicator Risk Assessment -- Thyroid Effects

Use Site	Pilots MOS Thyroid	Mixer/Loader MOS Thyroid
Apples	100-200	10-25
Cabbage	100-200	<10
Celery	100-200	<10
Cucumber	100-200	<10
Lettuce	50-75	<10
Peppers	100-200	<10
Potatoes	50-75	<10
Snap Beans	50-75	<10
Sweet Corn	50-75	<10
Tomatoes	300	<10
Watermelon	50-75	<10
Barley & Wheat	200	<10
Wild Rice	300	<10
Peanuts	300	<10
Sugar Beets	300-400	<10
Cotton	300-400	<10
Dry Beans	<10	---

short-term mutagenicity assays. Based on these studies ETU may be considered a direct mutagen in some bacterial and yeast assays, (probably acting by a base-substitution mechanism). However, ETU's genetic activity in bacteria must be considered rather weak. For example, in responsive base-substitution Salmonella strains customarily employed (TA 1535, TA 100), its potency (expressed as number of revertents per nanomole chemical) is less than 1/140,000 (i.e., 0.00069%) that of another direct-acting bacterial mutagen, captan. It is also difficult to reconcile its genetic activity in TA 1535 with negative results reported for the more sensitive sister-strain, TA 100 (Shirasu et al., in de Serres and Ashby, 1981). With regard to mammalian systems, ETU appears to show mutagenic activity. However, the capacity of ETU to transform mammalian cell cultures must be further tested in other cell lines and transformation systems in order to illuminate the mode of action of ETU and the EBDC's (e.g., by promotion or by initiation, and to interpret its oncogenicity in rodents (mouse hepatomas).

In summary, the available evidence for ETU indicates that it is mutagenic in certain bacterial strains, but the evidence is only slightly suggestive that ETU is mutagenic in mammalian systems. While no bacterial tests are needed at this time for ETU, one mammalian test (cell transformation assay) is needed for ETU.

6. Skin Sensitization

Skin sensitization or contact dermatitis is a condition of the skin resulting from previous exposure(s) in which a heightened reaction characterized by erythema, edema, pustular development, etc. develops from contact with a chemical. This response is thought to be mediated through the development of fixed antibodies in the skin. Circulating antibodies can be demonstrated in rare, very severe cases only. Thus, systemic anaphylactoid reactions in a person (or animal) having a skin sensitization are very rarely seen. While the eczematous dermatitis resulting in sensitized individuals can be very uncomfortable, it seldom interferes with work and will disappear upon removal of the offending chemical. Poison ivy dermatitis is the classic, familiar example (Woodard 1979).

Skin sensitization is one of the few phenomena in toxicology that usually can be experimentally evaluated directly in man. Human evidence, therefore, takes precedence in estimating probable hazard for man.

The literature available supports the conclusion that the EBDC's can elicit the skin sensitization in both guinea pigs and man. The California Departments of Health and Food and Agriculture annual tabulation of physician's reports of pesticide-related incidence should be a reliable guide to human exposure (Woodard 1979). In this study, the EBDC's are

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cited for approximately 1 percent of all dermal toxicity (9 of 711 cases). Based on these data, the Agency concludes that the EBDC's do not pose a substantial risk to humans. The label warns users of possible skin irritation and no further regulatory action is necessary.

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III. ANALYSIS OF BENEFITS

A. Introduction

The EBDC's are the most widely applied chemicals in the world for prevention of fungal diseases of plants used for the production of food in the United States. Specifically, EBDC's are used on many fruits, vegetables, and field crops, in addition to turfgrass, seeds, and ornamentals to control blights, blotches, mildews, molds, rots, rusts, and other diseases caused by fungi. No other commercial fungicides have as broad a spectrum on as many crops as those in the EBDC class. EBDC fungicides effectively control most of the major foliar pathogens of vegetables in the United States. Amounts of EBDC's used for major agricultural uses as well as industrial uses are given in Table III-1. Percentages of EBDC use for major agricultural crops are presented in Table III-2.

The EBDC's are widely accepted because they provide growers with a relatively inexpensive fungicide having few phytotoxic effects, give more effective control of certain fungal diseases, are compatible with most other commonly used pesticides, and are useful in combating the plant pathogens that have developed or are developing resistance to many of the more specific fungicides. In general, most of the agricultural crops previously treated with inorganic fungicides have shown substantial yield increases since being treated with EBDC's.

A major advantage of EBDC's is that they can be combined with other materials in tank mixes, thereby reducing the number of required applications on a particular crop and eliminating the cost of additional application. This advantage is significant in a state such as Florida, that is much more susceptible to fungal diseases because of hot temperatures and high humidity. EBDC's also are important in certain integrated techniques of pest management used on some crops. In apple production, for example, the EBDC's are compatible with spray oils and miticides, but they are not toxic to the natural predators of apple mites. As integrated programs of pest management become increasingly widespread, growers' need for selective and efficacious fungicides, which also minimize problems of pathogen resistance, will become increasingly more important.

Effective alternative pesticides are registered for most uses of EBDC's, but these alternatives are generally more expensive than the EBDC's. For example, potatoes, which are grown in every state within the continental United States (including Alaska), are exposed to late and early blight.

Table III-1. Amount of EBDC Active Ingredient Used in 1978

Crop	Pounds	Percentage
Potatoes	6,200,000	20
Small Grain	5,600,000	18
Apples	4,600,000	15
Cucurbits	3,249,000	11
Tomatoes	2,600,000	8
Peanuts	2,300,000	7
Onions	840,000	3
Sweet Corn	775,000	3
Turf	516,000	2
Citrus	500,000	2
Snap Beans	457,000	2
Pears	334,000	1
Celery	295,000	1
Lettuce	260,000	<1
Green Peppers	259,000	<1
Grass for Seed*		
Mushrooms	181,000	<1
Peaches	155,500	<1
Cabbage	110,000	<1
Christmas trees**		
Nursery stock	100,000	<1
Wild Rice	96,000	<1
Grapes	80,000	<1
Spinach	43,000	<1
Lima Beans	31,000	<1
Plums/Prunes	28,000	<1
Tobacco	26,000	<1
Almonds	22,000	<1
Nectarines	12,000	<1
Industrial uses	940,000	3
Total	30,611,930	

* Data not available. Rough estimate ranges between 160,000 and 480,000 pounds (<1%).

** Data not available. Rough estimate ranges between 80,000 and 114,000 pounds (<1%).

Source: EPA-USDA. 1979. Economic Assessment Report

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Table III-2. Percent of Crop Treated with EBDC

Crop	Percentage
Imported Bananas	100
Wild Rice	90
Mushrooms	63
Potatoes	53
Snap Beans	40
Sweet Corn	37.6
Apples	35
Cucurbits	35
Flowers, Foliage Plants	35
Spincah	35
Tobacco	33
Tomatoes	30
Lettuce	28.3
Onions	25
Pears	24
Green Peppers	22.2
Celery	20
Cabbage	20
Grass for Seed	18.5
Peanuts	14.4
Lima Beans	7.3
Citrus	5
Grapes	2.5
Peaches	3
Plums/Prunes	2
Small grain	1.8
Almonds	1
Nectarines	1
Cotton	0.06

Source: EPA/USDA. 1979. Economic
Assessment Report

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Captafol and chlorothalonil control early and late blight as well as, or slightly better than, EBDC's. The Assessment Team assumed that the cost of application and number of treatments were identical for each of these chemicals. The cost of the chemicals is the only difference in controlling these diseases. The cost per acre for each treatment is $3.00 for EBDC's, $3.80 for captafol, and $5.30 for chlorothalonil.

Because of differences in climate and, therefore, disease, the cost to producers of using the same alternative chemical may differ greatly. For example, the hot, humid climate of Florida is more conducive to fungal diseases than is the climate of California. An average of seven fungicide applications of either EBDC's or chlorothanoil would control early blight or late blight on celery in California, whereas an average of 20.2 fungicide applications of EBDC's or chlorothalonil would be necessary to control these same diseases on celery in Florida.

A major concern with respect to fungicides is the continuing problem of fungal resistance, which occurs with continued use of certain pesticides such as benomyl. Other alternatives, such as copper fungicides used on lettuce and spinach, are phytotoxic and may cause losses in yield and quality. (In this context, the term quality refers specifically to grade classifications established by USDA.) Table III-6 presents the relative costs of efficacy of the EBDC's and alternative means of control.

The benefits of the EBDC's have been evaluated in terms of the economic impacts that would result if EBDC uses were cancelled and users were forced to employ available alternatives.

Information concerning agricultural uses was provided by a USDA/State/EPA Assessment Team (EPA 1979; Ballard March 30, 1979; Pelletier 1978 and 1979). Information concerning industrial uses was provided by EPA reports (Mitre 1979; Pelletier 1978).

The Agency depends on the knowledge and expertise of the Assessment Team to estimate the major agricultural uses of EBDC's, to evaluate available data from a variety of sources, and to estimate economic effects from collected data on their best judgment. Many of the values used in the analysis are based on extrapolation from survey data and the experience of the Assessment Team members.

In computing changes in production costs, cost effects were based on estimates of most probable cases and judgments of the most likely alternative pesticide(s). Often the alternative(s) is the most efficacious and the most expensive. Data or estimates were not always available from which to determine the mix of alternative pesticides that would be used if EBDC's were cancelled.

Material costs were based on typical grower prices for 1977 and are compiled from price lists of various pesticide manufacturers. The Assessment Team based its assumptions on the percentage of each of the various alternatives that would be used on available data, on personal knowledge of disease control problems (many of the Assessment Team members were extension or research plant pathologists whose work was directly involved with disease control problems), on reports on pesticide uses and the pesticide market, and on communications with various state pesticide users.

In most cases, the projected agricultural use for 1977 was based on an average for the years 1974 through 1976. Dollar values for economic impacts are for 1 year and are estimated at a 1977 dollar value. Because of the variables in pesticide use, it was impossible to predict the availability of substitute chemicals or the future effects of their use on the economy.

Changes in consumer prices, where projected, were based on estimated changes in product prices due to the elasticity of demand for the product, the percentage change in production costs for the total United States crop, and the proportion of the total United States production affected by a cancellation of EBDC use for a given project. A more detailed analysis and discussion of the uses, alternatives, and economic impacts is available in the USDA/State/EPA Assessment Team Report (USDA 1978) and the Economic Impact Analysis document (EPA 1979). A summary of the economic impact to growers, should these uses be cancelled, is presented in Table III-3. Anticipated impacts to consumers are summarized in Table III-4. The analysis of economic impacts for industrial uses of the EBDC's is based upon a study conducted for EPA by the Mitre Corporation.

B. Use-by-Use Analyses of Benefits of EBDC's for Major Use Sites

1. Vegetables

a. Potatoes

The EBDC fungicides are registered and used for foliar treatment of potatoes to control blights and for treatment of

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Table III-3. Summary of Economic Impacts of Cancelling the EBDC Fungicides to Growers

Use Pattern	PRODUCERS ($ Million)
Tomatoes	10
Apples	10
Small Grains	8
Grass for Seed	8
Cuburbits	5
Sweet Corn	5
Potatoes	4
Wild Rice	3.2
Grapes	3.0
Peanuts	2.9
Mushrooms	2.5
Snap Beans	1.8
Tobacco	1.4
Celery	0.8
Christmas Tree (Nursery Stock)	0.6
Onions	0.5
Turf	0.45
Lima Beans	0.4
Flowers/Foliage Plants	0.4
Other Fruit	0.3
Cabbage	0.3
Plums/Prunes	0.05
Citrus	-8
Green Peppers	-5.7
Spinach	-10
Lettuce	-59

Source: EPA/USDA. 1979. Economic Assessment Report

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Table III-4. Summary of Economic Impacts of Cancelling the EBDC Fungicides to Consumers

Use Pattern	CONSUMERS ($ Million)
Lettuce	114.0
Spinach	17.8
Bananas	17.0
Green Peppers	7.4
Lima beans	3.0
Snap Beans	2.4
Cucurbits	1.0
Sweet Corn*	-16.0
Wild Rice	Unavailable
Total	$146.6

Source: EPA-USDA. 1979. Economic Assessment Report

*Assumes increased production if EBDC's are cancelled for use on lettuce.

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seed pieces against decays. About 53 percent of the United States commercial potato acreage is treated with EBDC's for blight; 51 percent of the acreage is treated with EBDC fungicides for seed piece decay.

The most likely substitutes for foliar treatment are captafol and chlorothalonil, which are as effective as EBDC for blight control (see Table III-6). Growers who replace mancozeb with these alternatives could experience increased costs in the range of $4.4 to $7 million annually, the most likely estimate being $4.6 million. This is less than 1 percent of the farm value of the potato crop (The 1975 farm value of the United States potato crop was about $1.3 billion.)

Captan is the alternative for treatment of seed pieces. Substitution of captan for EBDC's is not expected to affect the yield or quality of potatoes. However, use of this alternative would decrease production costs an estimated $100,000; it is not currently projected to affect significantly the retail prices of potatoes. Thus, the total loss of benefits from cancellation of use on potatoes is estimated to be about $4.5 million.

b. Mushrooms

Zineb is used on commercially grown mushrooms to control diseases known as dry bubble, wet bubble, mildew, and green mold. About 60 percent of the United States mushrooms are produced in Pennsylvania and 20 percent in California. Ninety percent of the crop grown in the western United States is treated; 60 percent of the eastern crop is treated. If use of zineb on mushrooms were cancelled, use of the only suitable alternative, benomyl would be increased (see Table III-6). Benomyl is not considered to be a viable alternative in the long run, however, unless benomyl is used in combination with zineb, the dry bubble fungus eventually develops resistance to treatment, rendering benomyl ineffective. In some cases, resistance has become apparent after only 9 months of continued benomyl use.

In the short run, use of benomyl as a substitute for zineb would produce adequate but more costly protection because treatment with benomyl is more expensive than zineb. Because resistance will build up against benomyl with time and because benomyl is the only alternative currently available, no long-term, viable alternative currently exists. If zineb were not available, losses in mushroom yield of between 9 and 13.5 percent would be expected because effectiveness of treatment is dependent upon continued intermittent use of zineb when benomyl resistance is encountered. Long-term losses in yield and quality costing between $2.5 to $3.5 million could occur as a consequence of EBDC cancellation. With no alternative to zineb available, a number of growers would find it impossible to remain in production. Consumers would be affected by higher prices and lower quality, particularly of fresh mushrooms.

c. Cabbage

Downy mildew and leaf spot diseases on cabbage are controlled by EBDC fungicides. Florida and California produce 18.3 and 7.8 percent, respectively, of the average annual United States production of cabbage. Ninety-two percent of the Florida crop and 40 percent of the California cabbage crop are treated with EBDC's.

If EBDC's were cancelled for use on cabbage, substitution of chlorothalonil would provide equivalent disease control and maintain the yields and quality of cabbage (see Table III-6). This would increase costs of treatment per acre by $14.92 in Florida and $5.70 in California, an average increase of $13.30. This represents additional total outlays of $262,000 for the two states, which would be borne primarily by those cabbage growers currently using the EBDC fungicides. The increase in production costs is not expected to significantly affect the retail market or consumer prices, since it is estimated to be less than 1 percent (0.7 percent) of the total production cost.

d. Cucurbit Crops

Approximately 260,000 acres of commercially grown cucurbit products (cucumbers, squash, pumpkin and melons) are treated annually with EBDC's for control of downy mildew, gummy stem blight, and target spot diseases. There are no effective nonchemical controls available for these diseases. Use of chlorothalonil and captafol can effectively control these diseases and maintain current yields and quality (see Table III-6).

Producers would incur increases in production costs per acre ranging from $9.98 for watermelons in Texas to $46.93 for squash in Florida. The increase in costs would total $5.5 million annually for all cucurbits. Cancellation of EBDC's would affect the prices for these commodities to a small degree. Consumer prices would not significantly increase except in the case of watermelons, the retail price of which is expected to increase 1.16 percent (an approximately $1.0 million annual increase). Estimates of use and impacts on squash production are based on Florida data only. The EBDC's are currently used in 100 percent of the Florida squash acreage. No data on United States squash production or on the percentage of United States squash production that is attributable to Florida are available. Likewise, data for cantaloupes are based on Texas production only.

e. Lettuce

EBDC's effectively control the most important disease of lettuce: downy mildew. This disease is prevalent in the three major lettuce-producing states--California, Arizona, and Florida--that produce 74, 15, and 3 percent of United States lettuce, respectively. Because of the high humidity in Florida's growing areas, conditions in that state are conducive to the development and spread of the disease and, therefore, require 100 percent of the lettuce acreage to be treated. Fifty percent of the Arizona lettuce acreage and 25 percent of the California lettuce acreage are treated with EBDC's. While copper is an effective alternative to EBDC's in Arizona and California, it is not suitable for treatment in Florida. In any case, copper damages lettuce, which results in reduction in grade and quality and eventually, dollar losses to the producers. The total impact of cancelling EBDC's in Florida, including the increased costs of using alternative pesticides and the yield loss resulting from the alternatives that are less efficacious is estimated as $659.20 per acre or 40 percent of the average annual revenue of 1975 to 1977. The extent of the impact of cancellation to Florida growers is difficult to assess because it is assumed that they would stop growing lettuce, since Florida accounts for only 3 percent of the total United States production (9,900 acres), and would eventually shift to an alternative crop, probably sweet corn.

In addition, cancellation of EBDC's on lettuce would negatively affect the yield, grade, and quality of the marketed crop. Yield would be reduced an estimated 12.5 percent in Arizona and California, and the quality of remaining lettuce (about one-fourth of all lettuce produced) would be reduced if growers were forced to use alternative means of control. Alternative registered fungicides for use on lettuce are not as effective and are seldom used (see Table III-6).

The initial impacts of cancelling EBDC fungicides for use on lettuce would result from the combination of yield and quality losses on lettuce grown in Arizona, California, and Florida. It is expected that yield losses of 12.5 percent in Arizona and California and 20.0 percent in Florida would cause Florida growers to discontinue lettuce production in favor of sweet corn due to lack of an effective alternative, while Arizona and California would continue lettuce production. The production on affected acreage in Arizona and California would, however, suffer quality declines valued at 12.5 percent. At current prices of $7.81/hundredweight, the value of the reduced production would be approximately $24 million.

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In the longer term, the combination of reduced production and quality changes would cause increases of both farm and retail prices. These price increases would bring new producers into lettuce production. An equilibrium would be reached with an estimated increase in farm prices of 14.7 percent to $8.96/hundredweight and a final decline in total lettuce production of about 1 percent. The net effect of the changes in price and production would be an increase in revenues to all lettuce producers of $59 million. This increase in revenue is the net result of losses on currently treated acreages and gains on nonaffected acreage. Losses on currently treated acreage are estimated to be $10.7 million ($273/acre) in California and $4.2 million ($221/acre) in Arizona. A $16.4 million decline in revenue will occur in Florida if farmers stop producing lettuce. The loss in Florida would be partially offset by revenues equalling $8.2 million from sweet corn grown in place of lettuce, giving a net decline of $8.2 million.

f. Celery

In California and Florida, EBDC's are used to control blights on celery. California and Florida produce 67.7 and 23.3 percent of the celery in the United States, respectively. About 20 percent of the California acreage and 100 percent of the Florida celery acreage are treated with EBDC's annually. Use of the preferred alternative, chlorothalonil, provides equivalent disease control and would maintain the yield and quality, but the cost of alternative chemicals per acre per season is higher (see Table III-6). Because of more severe disease pressure in Florida, fungicides must be applied 20 times per year as compared to 7 times per year in California. If chlorothalonil were used as the alternative pesticide, Florida users would incur increased production costs of 1.9 percent of revenue, or approximately $675,000, because fungi problems are more serious and require greater numbers of applications per season. California users would incur increased production costs equivalent to 0.5 percent, or approximately $85,000. Thus, the expected differences in material cost (chlorothalonil vs. EBDC) per acre would be about $21.61 in California and $62.44 in Florida. No significant impacts on the consumer or the retail market are anticipated as a consequence of cancellation of EBDC uses on celery because the quality and quantity of celery are expected to remain unchanged.

g. Onions

Approximately 38 percent of the United States commercially produced onions are grown in Texas, New York, Michigan, and California. About 25 percent of United States production of onions is treated with EBDC's to control three important diseases: downy mildew, purple blotch, and botrytis leaf blight. Anilazine and chlorothalonil are registered and

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recommended alternative chemicals that provide equivalent disease control and maintain yields and quality for onions (see Table III-6). When growers use the alternative chemicals, the increases in production costs range from 0.3 percent in California to 1.1 percent in Michigan, representing $8.08 to $24.51 per acre per season because of the higher cost per pound of active ingredient.

The estimated total annual increase in production costs are: Texas, $162,000; New York, $183,600; Michigan, $115,500; and California, $22,500. These increases should not cause significant shifts in cropping, market, or economic patterns and should not result in an increase in consumer prices for onions since no significant changes are expected in the quantity or quality of the commodity.

h. Snap Beans

Ninety-seven percent of Florida production (37,500 acres) of commercial green beans for the fresh market, representing 40 percent of the United States fresh-market production, is treated with EBDC's to control downy mildew, anthracnose, and rust diseases. There are no effective nonchemical controls available. Susceptibility to disease is greater in Florida, because of its climate, than in other states that produce snap beans. Commercial producers in other states do not use EBDC's extensively. In states other than Florida, beans are often produced for processing at a lower profit margin, and the use of fungicides is less economically attractive.

Chlorothalonil would provide equivalent disease control and maintain yields and quality when used as a substitute for EBDC's (see Table III-6). Because chlorothalonil is a more expensive fungicide than the EBDC's and requires a larger quantity of active ingredient per acre, the increased treatment cost in Florida would be fivefold or $49.00 per acre. Thus, cancellation of EBDC's is expected to cause a 7 percent increase in cost per acre for Florida growers, a 3 percent increase in annual costs of all United States production ($1,834,000) and a 2.24 percent increase in retail prices (or a $2,370,398 additional outlay by consumers).

i. Spinach

Downy mildew and white rust are rapidly spreading diseases of spinach and can destroy an entire field. There are no currently registered alternative fungicides to control these diseases if EBDC's were cancelled. However, chlorothalonil would effectively control these diseases if it were registered for use on spinach crops. Chlorothalonil is currently under review for this registration. Texas, Maryland, Virgina, and New Jersey produce about 43 percent of fresh-market spinach. For these states, 100 percent of the yield for those areas treated could be lost if EBDC's were

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cancelled and chlorothalonil were unavailable. About 35.5 percent (6,000 acres) of the United States fresh-market spinach is treated with EBDC fungicides, all of which could be lost if EBDC use were cancelled.

A cancellation of EBDC use on spinach would have a major impact on its price in the absence of chlorothalonil as an alternative. The extent of the increase in the price would depend on the reduction in quantity produced and on the responsiveness to price increases of quantities demanded and supplied. It is assumed that an EBDC cancellation without a registration of chlorothalonil would: 1) reduce the spinach supply at current prices by 35.5 percent, resulting in a 35.5 percent ($5,130,000) reduction in value of output; and 2) decrease production costs by $140,000. Hence, the initial impacts to producers of fresh-market spinach could approximate $5 million.

In Texas, spinach grown for processing instead of for fresh marketing is also treated with EBDC fungicides. To avoid disclosure of data pertaining to individual growers, precise acreage and production figures are not reported in either USDA or Texas state agricultural statistics. Combined data for Texas and Florida spinach produced for winter processing are available. However, on the basis of the 3-year average value (1975 to 1977) of $2.4 million in these two states and reports on production in Florida through the 1973 growing seasons, the value of the processing spinach grown in Texas is estimated at approximately $2 million per year. It is expected that spinach production for the processing market would cease if EBDC fungicides were cancelled and chlorothaonil were not registered, causing the immediate loss of benefits of about $2 million per year. The total loss from cancellation of EBDC use on spinach could, therefore, be about $7 million per year to producers of both fresh-market and process-market spinach.

However, spinach growers affected by an EBDC cancellation are likely to switch to alternative crops. In the face of potential yield losses approaching 100 percent in Texas, spinach producers in that state could be expected to shift 100 percent of their acreage to a more profitable alternative crop--probably onions. In the Maryland-Virginia area, spinach growers might be expected to switch 65 percent of current spinach acreage to soybeans. Likewise, in New Jersey, 65 percent of current spinach acreage might be switched to an alternative crop or crops. Although a number of crops would be plausible, cabbage is considered to be the most probable alternative crop in New Jersey. It is likely that a considerable portion of initial $7 million impacts to Texas, Maryland, Virginia, and New Jersey spinach producers would be balanced by profits gained from alternative crops. However, the extent of this reduction in losses could not be determined.

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In the longer run, the average annual consumer outlay for spinach, resulting from the decrease in quantity available and a constant demand schedule, could increase $17.8 million (from $64.1 to $81.9 million) in the absence of chlorothalonil. Cancellation of the use of EBDC fungicides on spinach could thus be expected to have a major impact on farm and consumer prices, with farm prices increasing by as much as 84.5 percent and retail prices increasing by as much as 56.8 percent. As a result of these price increases, United States growers who are nonusers of the EBDC fungicides, and who continue spinach production, could acrue increases in revenue estimated at $6 million.

j. Sweet Corn

EBDC fungicides are used on commercial sweet corn to control leaf blights and rust diseases. As much as 40 percent of the United States sweet corn is grown in Florida, where 97 percent (58,000 acres) of the acreage is treated with EBDC fungicides. Cancellation of EBDC's on lettuce might force current Florida lettuce growers into production of sweet corn, a more profitable crop than lettuce if EBDC's were not available for use. This shift in acreage from lettuce to sweet corn in Florida would increase the amount of sweet corn available to United States consumers. The impact of this increased supply of sweet corn would be a lowering of prices.

Use of the two favored alternative fungicides, captafol and chlorothaonil would provide equivalent disease control and the same quality and yield of corn as that attained with the EBDC fungicides (see Table III-6). Application costs and number of applications would remain the same but, because the alternatives are more expensive, the cost of chemicals per season would double ($1,400,000 increase). Total retail expenditures for sweet corn would decline about $16 million annually, and gross farm receipts would decline about $10 million annually for sweet corn as a result of the increased supply if use of EBDC on lettuce were cancelled. Corn growers in other areas would receive less for their product and would share in the $10 million decline in gross receipts.

k. Tomatoes

EBDC's are currently used on 30 percent of the tomatoes produced in the United States to prevent several diseases. The major tomato-producing states are Florida and California. Florida produces nearly 40 percent of the total United States fresh-market tomatoes; 96 percent of the acreage is treated with EBDC fungicides. California produced 33 percent of the fresh-market tomatoes and 83.6 percent of the processing tomatoes grown in the United States. EBDC's are used on 11 and 9 percent of the California fresh-market and process-market acreage, respectively. Ohio produces 6 percent of the U.S. production of tomatoes for processing; 99 percent of the Ohio acreage is treated with EBDC's.

Cancellation of EBDC's and use of alternative fungicides would have no significant national impact on the yields, grade, or quality of tomatoes (see Table III-6). Chlorothalonil and captafol are slightly more effective than EBDC's. Their use would maintain yields, grade, and quality, but because they are more costly, they would impose an increase in production costs of as much as $230.55 per acre in Florida, but less in other states. More applications are necessary in Florida due to its climate and the disease pressure. The additional applications represent an estimated weighted average increase of 1.95 percent in production costs. Cancellation of EBDC's is not expected to have any measurable impact on consumers.

The $10 million increase in growers' production costs may reduce the number of acres devoted to tomato production. There may be a shift to other crops, including sweet corn, potatoes, navy beans, and sugar beets.

l. Lima Beans

Lima bean acreage that requires disease control is primarily located in Delaware, Maryland, and New Jersey, where EBDC's are the recommended chemical for control of downy mildew. Copper is the only registered alternative; only two states list copper fungicides for alternative control, but copper does not give economical control of downy mildew. Downy mildew outbreaks in the mid-Atlantic states occurred 5 times during the 10-year period from 1968-1977. Approximately 60 percent of the lima bean acreage was treated with an EBDC fungicide during these outbreaks. When crops are untreated, losses as high as 50 percent of the yield could occur in 5 out of every 10 years. Average annual yield losses of $445,000 are anticipated, with a decrease in production costs of $75,000 due to discontinued use of the fungicide or discontinued production of lima beans ($380,000 net impact). The impact of cancellation of EBDC's would increase the nationwide consumer price of lima beans 2 percent. This would amount to an increase of $3 million per year in the price of processed lima beans.

m. Green Peppers

EBDC fungicides are used to control phytophthora blight, frogeye spot, and anthracnose on green peppers. In Florida, which accounts for 35.9 percent of United States production, 69 percent (12,811 acres) of the green pepper acreage is treated with EBDC's. Cancellation of EBDC's in Florida alone would affect 24.8 percent of the United States production.

Copper, the preferred alternative fungicide, is not effective against two of the important diseases; therefore, yields might decline as much as 19 percent if copper were used in place of EBDC's (see Table III-6). Growers would shift to other crops, depending on the decision to retain or to cancel EBDC use on other vegetables.

In the short run, 13.1 percent of the Florida production (5.2 percent of the United States production) would be lost, causing a long-run decrease of 1.6 percent of the total quantity of green peppers available and an increase of 14 percent in consumer prices after adjustments by growers. At current prices, the total loss to Florida growers would be $5.28 million; in addition, production costs would be increased $460,000 ($5,700,000 net impact). Growers not using EBDC's would realize a windfall gain due to an increase in consumer prices. The extent of simultaneous impacts was not determined by the Assessment Team.

n. Peanuts

EBDC fungicides are used to control leafspot diseases on peanuts primarily in four of the ten peanut-producing states. These states (Texas, Oklahoma, North Carolina, and Virginia) account for 37 percent of the total United States production. About 40 percent of the peanut acreage in these states (14.8 percent of the United States production) is treated with EBDC fungicides. EBDC fungicides represent only one of a number of possible alternatives (including benomyl, chlorothalonil and captafol, dodine, triphenyltin, copper, and sulfur) that can be used. Although the available alternative fungicides are not uniformly effective in disease control, it appears that cancellation of the EBDC fungicides would not have a major impact on the peanut industry. However, it has come to the Agency's attention that there is an increased incidence of secondary diseases in areas where chlorothalonil, captafol, or benomyl is being used.

Cancellation of EBDC's for use on peanuts would increase production costs less than 1 percent and would not significantly reduce peanut production. The total impact of an EBDC cancellation in the 4 affected peanut-producing states is estimated at $2.9 million. The economic impact, therefore, are not significant.

2. Fruits

a. Apples

EBDC's are used primarily to control apple scab disease in the eastern United States, where climatic conditions during critical periods of the growing season are conducive to fungal infection. Growers in other apple-producing areas are not currently dependent on EBDC's because they do not encounter serious problems from scab and because climatic conditions and varieties of apples grown are different. One-third of all United States apple acreage lies in the eastern United States, and about 85 percent of this acreage is treated with EBDC's. Captan and the EBDC's are considered necessary for the control of apple scab, where resistance to benomyl (the preferred alternative) has been encountered or can reasonably be expected to occur. EBDC's are particularly preferred because of their utility and value in the integrated programs of pest management and long-term control of "summer diseases" (a variety of fruit rots).

In the Southeast, a biological field test was conducted in North Carolina that demonstrated that up to 60 percent of the apple yield was lost when no fungal spray was used, 30 percent was lost when the alternative folpet was used, and only 2 percent was lost when EBDC spray was used. In the Southeast, use of alternatives such as folpet will increase user costs between $15.46 and $18.22 per acre, depending on the alternative used. The cost to apple producers in the Southeast would range from $1.1 to $2.6 million annually. The estimated loss of apples in the Southeast would be 96 million pounds, or 1.4 percent of the average yearly United States production. The total economic impact of EBDC cancellation for use in apples in the U.S. is estimated at $10 million per year ($7.7 million in loss of production and $2.2 million increase in cost for alternative fungicides). This loss is not expected to affect retail prices for apples because it represents a small percentage of the overall annual apple production, and apples can be held in storage and marketed on a national basis.

b. Bananas

EBDC's are used on bananas for the control of Sigatoka disease in the Central and South American countries that export to the United States. It is estimated that 100 percent of the bananas imported by the United States are treated with EBDC's. If EBDC tolerances for bananas were revoked, growers in the affected countries would either have to export their crop to other markets or adopt other materials or application schedules for control. Alternatives include benomyl, copper hydroxide, copper oxide, copper Bordeaux mixture, petroleum oil and thiophanate methyl. Due to the phytotoxic properties of some of these substitute pesticides (the oil sprays) and the fact that some diseases are resistant, especially to benomyl, growers would encounter problems in controlling these diseases. This would lead to estimated yield losses between 13 and 26 percent annually. The maximum total increase in consumer cost resulting from a cancellation of EBDC's is estimated at $17 million per year.

c. Citrus

Zineb is currently registered to control citrus rust mites and greasy spot disease, pests common to citrus crops in Florida and Texas. Greasy spot is not common to citrus trees in California, and it is virtually nonexistent in Arizona citrus. Currently there are no state recommendations for use of zineb on citrus because it has been characterized as an unreliable control for rust mites and greasy spot. Some entomologists have found that mites have developed a resistance to zineb and that it is no longer effective. Other fungicides have greater residual efficacy and are less costly and time-consuming to apply than zineb.

Chlorobenzilate and combinations with chlorobenzilate have been the most widely used miticides on Florida citrus (see Table III-6). The cost per acre of using zineb is $19.94 compared to $17.43 for benomyl, the preferred alternative for greasy spot, and $11.61 for chlorobenzilate, the preferred alternative miticide. The least expensive alternative is sulfur, which costs $2.67 per acre. Sulfur is very effective for short-term control, but over a long period its residue produces undersirable acidity of the soil. Cancellation of zineb would lead growers to substitute less expensive alternatives, resulting in savings of as much as $776 annually.

d. Pears

EBDC's are registered for use on pears to control two major diseases (fire blight and scab) and pear psylla, the most important insect pest of domestic pears. Approximately one-fourth of all United States-grown pears (25,000 acres) are treated with EBDC materials for control of pear psylla. Currently no other integrated program of pest management or cultural controls exists against this insect. Effective alternatives are very limited, although amitraz and some synthetic pyrethroid materials are now available on a restricted basis (see Table III-6). Amitraz, a relatively new insecticide and miticide formulated as BAAM EC, is used to control certain pests on apples and pears. The compound is now conditionally registered to control pear psylla. Prior to the conditional registration, the compound was temporarily approved under an EPA Section 18 Experimental Use Permit. The permit was granted on the basis that registered alternative pesticides were ineffective in some areas. Although the data base was small and variable, the weight of evidence indicated that without amitraz, overall fruit quality would decline progressively each year and trees would continuously be lost. As a result, growers would encounter sharp declines in production and consumers would be faced with increased prices for the commodity. Cancellation of EBDC's for use on pears for disease control would have a negligible effect, but cancellation of EBDC use against pear psylla would seriously hamper efforts to control this insect. The annual increase in grower costs resulting from a cancellation of EBDC's on pears is projected to be about $231,000. Potential reductions in yield exist, but their nature and extent are undetermined.

e. Grapes

EBDC fungicides are used to control diseases on grapes such a black rot, bitter rot, brown rot, ripe rot, dead arm, and downy mildew. Available alternatives, including captan, benomyl, and folpet, are less effective in controlling black rot, bitter rot, and downy mildew. In South Carolina and North Carolina, 95 and 55 percent, respectively, of the acres bearing muscadine grapes are treated annually. In Missouri, 40 percent of the bearing acres are treated annually. In California, the major grape-producing state, only 2 percent (12,100 acres) of the bearing acres are treated. Downy mildew is controlled best with EBDC compounds; registered alternatives are ineffective. The EBDC's are critical to production of 3,000 acres of muscadine grapes grown in the Southeast. Initially, 15 to 20 percent of the yield may be lost in the Southeast if EBDC fungicides are cancelled for use on grapes. In the long run, muscadine grape producers could be forced out of production because climatic conditions in the Southeast are conducive to the development of downy mildew. About 2.5 percent of the United States grapes are treated with EBDC fungicides each year. Cancellation of this use would result in an estimated loss of $2.3 to $3.1 million annually, or about 0.5 percent of the value of United States grape production. The impact on consumer prices would be minimal.

f. Plums (Including Prunes)

Two EBDC fungicides, zineb and nabam, are registered for control of various diseases of plums and prunes. Their use is generally limited to the East and Midwest, where black knot disease poses the most serious problem to plum and prune trees. Zineb is the perferred fungicide for control of black knot, particularly in Michigan, because the fungus has developed resistance to benomyl.

The 2,300 acres of plums treated with zineb represent approximately 2 percent of the United States and 18 percent of the Eastern acreage of plums. Since 91 percent of the plums produced in the United States are grown in California, the effect of cancellation of EBDC's for use on plums would be minor in terms of overall production. However, there would be regional impacts on production, particularly in Michigan and certain Eastern states where there are small acreages of plums. Cost to growers for replacement of trees damaged by black knot could be as high as $6,800,000.

Benomyl, the preferred alternative, provides acceptable control of the major diseases of plums for which EBDC's are registered unless resistance to the black knot fungus has developed (see Table III-6). However, cancellation of EBDC's and the possible development of fungal resistance to benomyl could leave growers without an effective fungicide against black knot. This condition could effectively eliminate all economic alternatives for control of black knot and certain other diseases. Since black knot is inevitably fatal to infected trees, this combination of circumstances may result in the abandonment of an estimated minimum of 4,000 acres of plum orchards in the affected regions. It is reasonable to assume that growers in these areas would shift to other fruit crops not afflicted with black knot. Cancellation of EBDC fungicides for use on plums and prunes would be expected to have little or no impact on consumer costs, since loss of the East and Midwest acreage would reduce total domestic production of plums and prunes by less than 4 percent. The initial yearly impact of cancellation of EBDC fungicides on plums and prunes is estimated at $48,000, an increase in the cost of treatment materials which would be borne by the growers. Long-range projections of costs are not considered in this amount.

3. Other Food Use

a. Wild Rice

EBDC's are applied as foliar protectants against leaf spot diseases on 90 percent of the wild rice acreage. Treatment is essential because leaf spot diseases can wipe out the yield in some years. There are no registered alternatives that control leaf spot diseases on wild rice.

Wild rice is a minor crop grown only in Minnesota. Because of rotations with other crops, approximately 65 percent of the acreage (15,000 acres) capable of producing paddy rice is cultivated in a given year. EBDC's provide low-cost, efficacious protection. Each year $200,000 worth of EBDC fungicides is applied to commercial (paddy) wild rice grown in Minnesota. Cancellation of EBDC's would have major impact on the yield of cultivated rice and would adversely affect the value of "wild" lake rice, an important income source for reservation Indians. Yields would be expected to decline about 15 percent ($3,400,000) annually. Cancellation of EBDC's for use on wild rice would result in a significant price increase for this commodity in order to make production economically feasible, or the crop would no longer be grown commercially.

b. Small Grains

EBDC fungicides are applied as foliar protectants to 1.4 million acres of cereal grain to prevent leaf spotting diseases for which there are no effective alternatives. Approximately 1.5 percent of the wheat and 4.6 percent of the barley acreage in the United States are treated with EBDC's. If EBDC uses on grains were cancelled, the United States wheat and barley production would decline 0.33 and 1.01 percent, respectively. The annual yield loss is estimated at $27,650,000, and the decrease in treatment costs is estimated at $18,872,000 (giving a net impact of $8,800,000). If the disease were severe enough to eliminate the entire production on the acreage currently treated with EBDC's, United States wheat and barley production would decline approximately 1.5 and 4.6 percent, respectively. Even in this "worst case" situation, the reductions in wheat and barley supply would cause only minor changes in consumer prices.

c. Sugar Beets

Three of the EBDC fungicides are registered for control of leaf spot disease; one is also registered as a seed treatment of control damping off in sugar beets. About 5 percent of the total acreage (1.5 million acres) is treated for leaf spot in a given year. Only 10 percent of the sprayed beet acreage (less than 10,000 acres) is treated with EBDC's. Few acres are treated because growers use resistant varieties and tolerate loss from the disease. Treatment is often not initiated until epidemics develop. A single application of the highly effective benzimidazole fungicides can contain an epidemic (see Table III-6). The benzimidazole fungicides are as effective as, or more effective than, EBDC's in controlling leaf spot. The only potential problem associated with their use is that resistant strains of the pathogen can develop.

4. Cotton

Mancozeb is used to prevent and to control Southwestern cotton rust on extra-long staple cotton grown mainly in Texas, Arizona, and New Mexico. Since a very small percentage (0.06 percent, or 8,000 acres) of the United States cotton crop is treated with mancozeb, cancellation is expected to have a negligible economic effect on the cotton market. An economic analysis of the use of EBDC on cotton was not considered necessary.

5. Tobacco

Diseases including anthracnose, blue mold, and "damping off" are controlled on flue-cured, burley, and Maryland tobacco by use of EBDC fungicides. Nonchemical controls, in conjunction with chemical controls, are recommended in many of the tobacco-producing states for control of blue mold. EPA estimated that 44.7 to 56.8 percent of the flue-cured tobacco seedbeds were treated with EBDC's in 1977. EBDC's

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are used most extensively on flue-cured tobacco grown in North Carolina and Virginia. Smaller quantities are used on burley and Maryland tobacco.

Given conducive weather conditions, blue mold is the most destructive of the diseases that attack tobacco. To protect tobacco crops against blue mold as well as anthracnose and "damping off," a preventative program of twice-a-week seedbed applications (spray or dust) of fungicides containing ferbam, zineb, maneb, or metiram was developed in North Carolina in the late 1940s. North Carolina growers used the preventative program extensively during the forties, fifties, and early sixties. Blue mold was not considered a major disease during the late sixties and early seventies and, therefore, fungicide use dropped to a low level. In 1979, however, blue mold returned as a field problem and caused extensive damage in all types of tobacco in the United States and Canada with the exception of cigar binder in Wisconsin. Likewise, mold was widespread in plant beds in 1980, and extensive field damage occurred in unprotected fields. Use of the preventative program in the bed site increased from less than 40 percent in 1979 to more than 95 percent in 1980 (Todd 1980).

As an alternative to the EBDC's, streptomycin sulfate provides good blue mold protection but is not effective in control of anthracnose and damping off. In the event of a disease epidemic, the ready availability of adequate amounts of streptomycin sulfate, which is normally used in relatively small volumes in agriculture, is questionable (Todd 1980).

Metalaxyl, applied at 1 to 2 quarts per acre as a soil incorporation treatment, provides full season protection, but is more expensive than the EBDC's. Unlike the EBDC's, Metalaxyl must be applied before there is a known threat of an outbreak. Because the blue mold fungus has already shown resistance to Metalaxyl, an EBDC-type fungicide will probably be needed in programs with Metalaxyl to avoid a resistance problem (Todd 1980).

A third alternative, ferbam, is used by many growers. Twice as many ferbam applications as EBDC fungicide applications are sometimes needed to achieve equivalent disease control. In some areas, when anthracnose is severe, use of alternative chemicals could result in 5 percent yield loss in the seedbeds. The annual estimate of yield loss is $1,100,000; increased treatment costs are estimated between $28,000 and $337,000, for a projected annual cost of about $1,400,000.

Notwithstanding an exceptionally severe disease epidemic, lack of availability of EBDC's is expected to have only slight market impact because a price support program and market quota system exist. The possibility of such epidemics must be acknowledged, however, in view of the example of 1979, when widespread blue mold damaged crops in the United States and Canada. Overall losses to growers amounted to $250 million (9 percent reduction in crop value and cost). Since 10 percent of the value of a pack of cigarettes is the cost of tobacco, only very significant increases in the value of tobacco would have an impact on the consumer level.

6. Ornamentals

a. Christmas Tree Plantations and Pine Nurseries

Pine needlecast disease affects red pine and Scotch pine, the best-selling species for Christmas trees. Mancozeb controls 95 percent of this disease. Chlorothalonil, the only other chemical registered for control of this disease, is less effective (87 percent control) and costs twice as much to use. Data for efficacy in nursery use are not available.

The disease appears in the Pacific Northwest states and those states surrounding the Great Lakes. The USDA/State/EPA Assessment Team estimated that 10,000 acres of Christmas tree plantations in those areas, a possible 6 percent of all acres of Scotch and red pine, are treated each year. Nursery customers would notice an increase in price, due to a decrease in the availability of red and Scotch pine seedlings, if EBDC's were cancelled for use on these species. Christmas tree buyers would also experience higher prices and decreased supplies of Scotch pine. The extent of this impact cannot be determined because data are limited and grower and consumer responses are uncertain.

The annual cost of discontinuing use of EBDC's on Christmas trees is expected to be $500,000 to $587,000 in yield losses and increased chemical costs. The cost of discontinuing use in nurseries, excluding commercial nurseries, is estimated between $20,000 and $42,000. Data on the number of commercial nurseries are not available. Records are available only from the U.S. Forest Service and Washington state. Estimates were projected on this basis and are speculative.

b. Floral and Ornamental Crops

EBDC fungicides are used against numerous specific fungal diseases of floral and ornamental plants. For example, zineb is registered for control of 69 diseases. Their widespread efficacy makes EBDC's particularly useful to growers who specialize in a variety of crops in the warm, moist regions where numerous fungal diseases are prevalent. The EBDC fungicides ensure the commercial grower a means of adequate, nonphytotoxic control of a wide variety of fungi. This reliability reduces the uncertainty of the grower's income, regardless of climatic conditions.

It is expected that alternative fungicides or combinations of fungicides will provide protection equal to that of EBDC's though at different costs (see Table III-6). Although no quantitative analysis was practicable in overall terms, available data have enabled the Agency to project the impact of an EBDC cancellation on growers of gladioli and chrysanthemums: approximately $357,000.

c. Turfgrass

Due to the large number and wide variety of uses (home lawns to golf courses), the wide geographical dispersion, and the intermittent use (ranging from 1 to 10 applications of EBDC's on turfgrass), very little consistent data are available concerning the actual application of EBDC's to control turfgrass diseases. When applied at the appropriate rates, alternative fungicides are as effective as EBDC's (see Table III-6.) They are, however, more costly. Alternatives cost $1.50 per 1,000 square feet, whereas zineb costs $0.17 per 1,000 square feet (a difference of about $450,000 per year, nationwide). The increase in expenditure for the alternative fungicides makes up such a small part of the total cost of maintaining turfgrass for home lawns, athletic fields, and golf courses that cancellation of EBDC's probably will not affect the decision on the use of alternative fungicides for disease control.

d. Grass for Seed

In Oregon and Washington, EBDC's are used to control rusts and other foliar diseases of turfgrass grown for seed (50,000 acres). Control of disease by burning is being eliminated by legislation controlling air pollution. Without treatment, yields are estimated at one-third the yields of treated acreage. The value of the treated Washington-Oregon crop is estimated at $14 million. Grass yields were estimated by the Assessment Team to be 400 to 1,000 pounds per acre when treated with maneb and 100 to 300 pounds per acre without such treatment. The estimated effect of cancellation is an $8 million loss in yield. No acceptable alternative currently is registered for control of rust disease.

7. Industrial Uses

Nabam is used to control algal, bacterial, and fungal growth in water-cooling systems, sugar mills, and pulp and paper mills. Uncontrolled growth of the organisms in water systems can contaminate the final product and hinder operation of equipment. Numerous alternatives are registered for all sites except sugar mills. Registered biocides for sugar mills are limited to two products containing calcium hypochlorite and two products containing combinations of chemicals. From the available data, nabam appears to represent between 2 and 3 percent of all biocides used for these industrial sites. The number of applications, rates of active ingredient applied, and the methods of application are summarized in Table III-5.

a. Cooling Towers

Nabam is one of 33 active ingredients used mainly at utility and industrial cooling towers requiring a high volume circulation rate for condensation of steam and for process cooling and refrigeration. It is estimated that between 297,000 and 305,000 pounds of nabam are used each year at these sites.

Many pesticides are used jointly or in combinations, so that efficacy of any one is difficult to determine. There are no effective mechanical means for controlling fungal growth in water systems. Two major categories of biocides are used: oxidizing microbiocides, such as chlorine and ozone, and nonoxidizing biocides such as the chlorinated phenols, quarternary ammonium compounds, and organo-sulfur compounds.

Cancellation of EBDC (nabam) use would likely have a negligible economic effect due to the manner in which it is used with various other biocides and the number of available alternatives. Some alternatives are more costly, but their use is not expected to produce a significant economic impact.

b. Evaporative Condensers

All microbiocides used for cooling towers can probably also be used in evaporative condensers because, with respect to water treatment, there are no significant differences between the two. It is estimated that during 1978 10,000 pounds of nabam were used in evaporative coolers. Eight-five to 99 percent was added by hand methods.

Although nabam is widely used for control of fungi and bacteria found at evaporative coolers, there are several other active ingredients that are alternatives. Other active ingredients include copper sulfate monohydrate, isopropanol, and didecyl dimethyl ammonium chloride. Manual cleaning is also an alternative method for control at some sites. Sodium pentacholorophenate and 2,4,5-trichlorophenol and its salts, two of the alternatives, are currently under RPAR review. It is very unlikely that cancellation of these use of EBDC's would cause serious, adverse economic impact.

Table III-5. Rates and Methods of EBDC Applications -- Industrial Uses

Site	Number of Applications/Rates/Methods
Cooling Towers	Usually "shot" fed as one dose of 3-6 ppm.
Air Washers	Initial high concentration dose of 8-15 ppm once a day for a week or every several hours for a few days. Subsequent doses "as needed" (once or twice per week) of 4-8 ppm.
Evaporative Condensers	Initial high concentration dose of 36 ppm for 3 days, followed by 6-12 ppm in subsequent doses "as needed."
Pulp and Paper Mills	Applied to water at the rate of 60-80 milliliters per minute during the day, two hours a day, or for 30 minutes every 12 hours.
Sugar Mills	Drip fed at the rate of 10-20 ppm of cane ground per day.

Source: Mitre Corp. 1979. Use Profiles and Alternatives Assessment for Nabam 2,4,5-Trichlorophenol (2,4,5-TCP) and Pentachlorophenol (PCT) for Industrial Water Treatment. EPA Contract #68-01-3965.

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c. Air Washers

Nabam is registered for use in air washers to prevent fouling of the water by fungi and bacteria. It is estimated that 45,000 pounds were used in 1978. For use in air washers, alternatives must not cause foul orders that discomfort workers or contaminate the finished product. Pentachlorophenol and its salts (35,000 pounds in 1978) and 2,4,5-trichlorophenol and its salts (6,000 pounds in 1978), are alternatives. Carbamates are acceptable for use in tobacco processing plants, but not in textile manufacturing facilities. Quarternary ammonium compounds are efficacious, but they cause the water to foam. Chlorine derivatives give rise to foul odors and corrode equipment.

Only a few of the registered alternatives are satisfactory substitutes for nabam for use in air washers. Cancellation of EBDC's could, therefore, cause adverse economic impacts on users of nabam, though impacts are expected to be relatively insignificant.

d. Pulp and Paper Mills

Most slimicides used in pulp and paper mills are applied by chemical company representatives and are used in combination with other compounds (one to four slimicides at a time). They are usually applied directly in the pulp slurry or the "white' water system by single applications, continuous feeding, or intermittent feeding. It is estimated that between 10 and 50 percent of the paper and pulp mills use nabam, with an estimated 25 percent of the mills using 225,000 pounds in 1978.

Alternatives used include a wide variety or organo-sulfur compounds, nitrogen compounds, bromine compounds, chlorinated phenols, and acrolein. Cancellation of nabam is not expected to have significant economic impacts.

e. Sugar Beet and Cane Mills

Nabam is used in approximately 60 percent of the cane and beet sugar mills. The number of mills using nabam at any given time depends on the volume of operation. When sugar prices are high, the volume of operation is high. During peak operation of sugar mills, nabam is used to control fungal growth as a temporary measure so that the mill does not have to shut down its operations to clean equipment. Nabam is applied in a liquid formulation as a metered continuous drip feed at the rate of 10 to 20 ppm in cane ground per day. Sugar mills operate on a seasonal basis; cane mills operate from October to January or February, and beet mills run from October to March.

Four alternative chemicals are used either singly or in combinations: calcium hypochlorite, potassium N-methyldithiocarbamate, disodium cyanodithioimido-carbonate, and ethylene diamine. Economic impacts of cancellation of EBDC use in sugar mills do not appear to be very significant. Sugar millers contacted did not express great interest in nabam-containing products, although about 360,000 pounds are used annually in sugar mills.

Table III-6. Selected Alternati hemicals Available to Replace EBDC

Crop	Registered Chemicals	Cost/Acre Use (in Dollars)	Non-Chemical	Efficacy
Vegetables				
1. Cabbage	chlorothalonil, copper	EBDC: 11.21 (FLA) 7.60 (CA) chlorothalonil: 26.13 (FLA) 13.30 (CA)	No known non-chemical controls.	Chlorothalonil equivalent to EBDC.
2. Cucurbits	benomyl, captafol, chlorothalonil	Cost varies for type of cucurbit and state in which chemical is used.	No known non-chemical controls.	Chlorothalonil equivalent to EBDC, captafol equivalent to EBDC, for cantaloupes in Texas.
3. Potatoes	captan, captafol, chlorothalonil triphenyltin hydroxide, dyrene, copper	EBDC: 4.15 (seed piece) 3.00 (foliar) captafol: 3.80 (foliar) chlorothalonil: 5.30 (foliar) captan: 4.68 (seed piece)	No known non-chemical controls.	Captafol and chlorothalonil control early and late blight equivalent to EBDC. Captan equivalent to EBDC in seed piece treatment.*
4. Lettuce	captan, folpet copper	copper: 8.75 (CA, AZ) 0 (FLA) EBDC: 7.60 (CA) 7.60 (AZ) 5.32 (FLA)	No known non-chemical controls.	Copper effective against downy mildew in Arizona and California but has phytotoxic results. Captan and folpet do not control downy mildew in lettuce for commercial purposes.
5. Celery	benomyl, chlorothalonil anilazine, copper	EBDC: 15.96 (CA) 45.98 (FLA) chlorothalonil: 37.57 (CA) 108.44 (FLA)	No known non-chemical controls.	Chlorothanlonil equivalent to EBDC.

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* EBDC more effective against fusaria, captan equal to or better than EBDC for rhizoctonia. Variable effectiveness of captan and EBDC against scab.

Table III-6. Selected Alternative Chemicals Available to Replace EBDC (Continued)

Crop	Registered Chemicals	Cost/Acre Use (In Dollars)	Non-Chemical	Efficacy
Vegetables (Continued)				
6. Mushrooms	benomyl	Benomyl: application 0.22 - .24 EBDC: 0.12 - .13	No known non-chemical controls. application	Questionable effectiveness when not combined with EBDC.
7. Onions	chlorothalonil anilazine	chlorothalonil: 21.38 (TEX) 47.98 (NY) 42.75 (MICH) anilazine: 24.94 (CAL) EBDC: 13.30 (TEX) 27.36 (NY) 18.24 (MICH) 15.96 (CAL)	No known non-chemical controls.	Dyrene and chlorothalonil provide equivalent control.
8. Snap Beans	chlorothalonil	chlorothalonil: 62.22 EBDC: 13.22	No known non-chemical controls.	Chlorothalonil provides equivalent control for rent.
9. Spinach	captan, copper chlorothalonil	not used: 13.68 (TEX) (NJ)	No known non-chemical controls.	Copper and captan do not provide economic control in heavily affected areas.
10. Sweet Corn	captafol, chlorothalonil	EBDC: 25.31 chlorothalonil, captafol: 49.96 (combined)	No known non-chemical controls.	Chlorothalonil and captafol provide equivalent control.
11. Tomatoes	captan, captafol, chlorothalonil, anilazine	chlorothalnil: 230.85 (FLA) 38.00 (CAL) 76.00 (SC) 66.50 (ALA) 57.00 (NJ) 76.00 (MICH) 47.50 (NY) 38.00 (GA) 57.00 (VA) 57.00 (MD) 95.00 (NC)		

Table III-6. Selected Alternative Ch cals Available to Replace EBDC (Contin)

Crop	Registered Chemicals	Cost/Acre Use (in Dollars)	Non-Chemical	Efficacy
Vegetables (Continued)				
11. Tomatoes (Cont.)		EBDC: 61.56 (FLA) 15.20 (CAL) 21.28 (SC) 26.60 (ALA) 22.80 (NJ) 24.32 (MICH) 22.80 (NY) 12.16 (GA) 27.36 (VA) 27.36 (MD) 22.80 (NC)		
12. Lima Beans	copper	EBDC: 6.08 copper: Not used.	No known non-chemical controls.	Copper does not give economic control of downy mildew in heavily affected states (DEL., MD, NJ)
13. Green Peppers	captan, copper	EBDC: 17.33 copper: 53.20	No known non-chemical controls.	Copper effective only against frog eye spot. Not effective against anthracnose or phytophora blight.
Fruits				
1. Apples	benomyl, captan, folpet, captafol, thiram, dinocap, sulfur, coppers, dodine, ferbam	EBDC: 11.76 benomyl: 10.95 oil: 2.28 thiram: 12.96 dinocap: 15.28 captan: 49.49	Removal of drops. Pruning infected limbs. Removal of infected trees. Cultural practices alone do not provide adequate control.	Alternatives equally effective with EBDC in Northeast, Mid-Atlantic, Midwest. In Southeast alternatives not as effective due to disease complex.
2. Bananas	benomyl thiophanate-methyl, petroleum oils, coppers (Honduras)	Data not available.	Data not available.	Yields to remain constant with alternatives short term except in Honduras. Phytotoxic results of copper use in Honduras.

Table III-6. Selected Alternative Ch[illegible]cals Available to Replace EBDC (Contin)

Crop	Registered Chemicals	Cost/Acre Use (in Dollars)	Non-Chemical	Efficacy
Fruits (Cont.)				
3. Pears	benomyl, captan, captafol, dodine, ferbam, amitraz, endosulfan, phosmet	EBDC: 10.50 benomyl: 16.50 captan: 10.00 amitraz: 38.50 endosulfan: 18.00 phosmet: 8.00	Orchard sanitation practices aid in preventing spread of disease, but do not control once disease is established. No IPM or cultural control for pear psylla.	Benomyl most effective where resistance has not occured.
4. Plums	benomyl, captan (including prunes) captafol, thiram, bordeaux, copper, dichlone, dichloran, ferbam, sulfur	EBDC: 6.53 benomyl: 12.45 captan: 6.48 dichlone: 6.24 ferbam: 5.67 sulfur: 2.68	Orchard sanitation practices. Removing wild cherry trees aids in preventing disease spread.	Benomyl most effective where resistance has not not occurred.
5. Citrus	benomyl, chlorobenzilate, copper, oil, sulfur, ethion	EBDC: 19.94 benomyl: 11.43 copper: 4.80 oil: 10.30 chlorobenzilate: 11.61 sulfur: 2.67 ethion/oil: 16.71	Removing leaf litter prevents medium for growth of grease spot. Predacious mites and insects used to kill citrus rust mites.	Benomyl best control for greasy spot. Copper and oil have drawbacks to growers but control greasy spot. Chlorobenzilate controls mites. Sulfur effective against mites for short period.
6. Nectarines	benomyl, captan, thiophanate-methyl, bordeaux, calcium polysulfide, coppers, dichlone, dichloran, ferbam, sulfur	EBDC: 10.00 captan: 7.50 dichloran: 14.00	Orchard sanitation practices aid in preventing spread of disease but do not control once established.	Benomyl effective where resistance has not occurred. Dichloran and captan are other major alternatives.
7. Peaches	benomyl, thiophantemethyl, bordeaux, calcium polysulfide, coppers, dichlone, ferbam, sulfur	EBDC: 10.00 captan: 7.50 dichloran: 14.00	Orchard sanitation practices aid in preventing spread of disease but do not control once established.	Benomyl effective where resistance has not ocurocurred. Dichloran and captan are also effective.
8. Almonds	benomyl, captan, bordeaux, coppers, dichlone	EBDC: 10.50 benomyl: 16.50 captan: 7.50 dichlone: 11.14	Orchard sanitation practices aid in preventing spread of disease but do not control once established.	Benomyl effective where resistance has not occurred.

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Table III-6. Selected Alternative Ch cals Available to Replace EBDC (Conti.)

Crop	Registered Chemicals	Cost/Acre Use (in Dollars)	Non-Chemical	Efficacy
Fruits (Cont.)				
9. Pecans	benomyl, dichloran, triphenyltin hydroxide	Data not available.	Orchard sanitation practices aid in preventing spread of disease but do not control once established.	Benomyl effective where resistance has not occurred.
10. Grapes	benomyl, captan, folpet, ferbam	EBDC: 3.14 benomyl: 4.15 ferbam: 2.16 captan: 2.16 folpet: not available	No known non-chemical controls.	Captan, benomyl, folpet less effective than EBDC against fruit rots, especially in Southeast.
11. Apricots	benomyl, captan, captafol, sulfur, coppers	EBDC: 10.50 benomyl: 16.50 captan: 7.50	Orchard sanitation practices aid in preventing spread of disease but do not control once established.	Benomyl most effective where resistance has not occurred.
12. Cherries	benomyl, captan, captafol,	Data not available.	Orchard sanitation practices aid in preventing spread of disease but do not control once established.	Benomyl most effective where resistance has not occurred.
Ornamentals				
1. Christmas tree plantations and pine nurseries	chlorothalonil	(Christmas trees) EBDC: 14-18 (East) 22-40 (PNW) chlorothalonil: 28-38 (East) 44-84 (PNW) (Pine Nurseries) EBDC: 18-35 (East) 22-40 (PNW) chlorothalonil: 38-75 (East) 44-84 (PNW)	Alternating blocks of species. Use of sanitation measures.	Chlorothalonil gives 87% control for Christmas trees compared to 95% control from EBDC. Non-chemical controls lessen severity but do not control disease.

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Table III-6. Selected Alternative Ch[illegible]cals Available to Replace EBDC (Conti[illegible]d)

Crop	Registered Chemicals	Cost/Acre Use (in Dollars)	Non-Chemical	Efficacy
Ornaments (Cont.)				
2. Floral and ornamental crops	benomyl, chlorothalonil (chrysanthemums), ferbam (gladioli)	EBDC: 3.74 benomyl: 12.00 chlorothalonil: 9.90 ferbam: 3.24	No known non-chemical controls.	Alternatives perform equally as well as EBDC.
3. Turfgrass*	benomyl (rhizoctonia), thiophanate-methyl (rhizoctonia),	EBDC: 0.17-0.66 cycloheximide: 0.45	No known non-chemical controls.	Alternatives perform equally as well as EBDC.
	cycloheximide PCNB (rhizoctonia), thiram (rhizoctonia), chlorothalonil (rhizoctonia, helminthosporium) anilazine (rhizoctonia, helminthosporium), chloroneb (pythium), ethazole (pythium), fenaminosulf (pythium)	thiram: 0.58 chloroneb: 1.50 fenaminosulf: 1.41 chlorothalonil: 0.89 anilazine: 0.92		
4. Grass for seed	nickle sulfate	EBDC: 2.05-3.07	Field burning (being eliminated because of air pollution rules).	Nickle sulfate much less effective than EBDC.
Field Crops				
1. Peanuts	benomyl, captafol, chlorothalonil, chlorododine, triphentin, copper, sulfur	EBDC: 15.96 chlorothalonil: 26.60	No known non-chemical controls.	Chlorothalonil comparable to EBDC.
2. Tobacco	ferbam, streptomycin metalaxyl	EBDC: 1.04-1.30/100 sq. yds. ferbam: 1.30-2.60/100 sq. yds. streptomycin: 1.60/100 sq. yds.	Blue mold partially eliminated by growing under plastic and rotating bed sites.	Ferbam controls with one or two applications (except in Maryland). Streptomycin effective against blue mold in Maryland.

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*Cost per 1000 square feet.

Source: EPA-USDA. 1979. Economic Assessment Report.

Table III-6. Selected Alternative Ch[illegible]cals Available to Replace EBDC (Contin[illegible])

Crop	Registered Chemicals	Cost/Acre Use (in Dollars)	Non-Chemical	Efficacy
Field Crops (Cont.)				
3. Wild Rice	None	EBDC: 21.57	No known non-chemicals controls.	Not applicable.
4. Small Grains	Sulfur Copper oxide	EBDC: 13.48	No known non-chemical controls.	Not applicable.
5. Sugar Beets	benomyl (cercospora leafspot), PCNB (rhizoctonia), benzimidazole, "Duter" (rhitoctonia, cercospora leafspot)	Data not available.	Breeding resistant strains of tobacco.	Benomyl effective against cercospora leafspot except where resistance occurs. Benzimidazole and "Duter" are are as efficacious as EBDC.
6. Cotton	captan, sulfur	Data not available.	No known non-chemical controls.	Sulfur not currently used.

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IV. REGULATORY OPTIONS

Three basic regulatory options have been developed:

(1) Continue registration without additional restriction.

(2) Continue registration but amend the terms and conditions of registration.

(3) Cancel registration.

Cancellation of registration (Option 3) and continued registration (Options 1) represent absolute regulatory responses. Registration with amended terms and conditions (Option 2), however, represents a range of possible courses of action that are aimed at reducing risks rather than cancelling uses or taking no action. Risk reduction measures were considered and evaluated for their potential effectiveness and feasibility as follows.

A. Measures to Reduce Dietary Exposure

Amounts of pesticide residues on food crops are affected by quantity of active ingredient used, the solvents used for dilution, mode and schedule of application, preharvest interval, and soil and weather conditions. Several measures were considered as means by which dietary exposure to ETU through residues on food crops might be reduced.

1. Preharvest Intervals (PHI's)

Dietary exposure due to ETU residues on food crops might be reduced if preharvest intervals (PHI's) were extended. On any given crop, the PHI is the number of days that must elapse between the final application of an EBDC fungicide and actual harvest. Extending PHI's allocates additional time for dissipation of residues before crops are harvested--all other factors, such as weather conditions, being equal. Extending PHI's can serve as a means of lowering tolerances.

Current PHI's for EBDC uses vary widely, ranging from 0 to in excess of 66 days, depending upon crop and geographical region. The implementation of extended PHI's as a risk-reduction measure would necessarily proceed on a use-by-use basis, taking regional considerations into account as well as the availability of suitable alternative fungicides that might be used in place of the EBDC's for final applications. When the established residue tolerances for major crops were reduced in 1972, the PHI was increased to ensure that any fungicide residue remaining on the crop would not exceed the lower tolerance.

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At this time, however, extended PHI's cannot be pursued as a viable option in the absence of dietary exposure/residue data that would enable the Agency to determine the extent to which dietary exposure might be reduced. Until the necessary data become available, an informed risk/benefit analysis of this particular option is not possible, and extended PHI's as means to reduce dietary exposure and risk are impracticable. However, PHI's could be highlighted on labels so that homeowners will be encouraged to follow current PHI's.

2. Modify Application Practices

There is the possibility that dietary exposure due to ETU residues on food crops could be reduced if current application practices were modified. Specifically, two possibilities have been considered: (1) combining EBDC with an alternative fungicide in tank mixes, and (2) alternating applications of EBDC with applications of an alternative fungicide, thereby reducing the total amount of the EBDC's used on agricultural crops. These modified application practices--like extended PHI's--might enable tolerances to be lowered.

Either of these modifications would necessarily proceed on a use-by-use, region-by-region basis, taking into account multiple factors, including the availability of suitable alternative fungicides, as well as questions of pathogen resistance, phytotoxicity, susceptibility of crops to diseases, regional severity of diseases, spectrum of disease control required, and weather conditions. In connection with the possibility of EBDC/alternative fungicide mixtures, compatibility of fungicides is also at issue (Pelletier, 1979).

At this time, however, modified application practices cannot be pursued as a viable option in the absence of dietary exposure/residue data that would enable the Agency to determine the extent to which dietary exposure might be reduced. Until the necessary data become available, an informed risk/benefit analysis of this particular option is not possible and modified application practices as means to reduce dietary exposure are impracticable.

3. Employ Integrated Pest Management (IPM) Techniques

It is possible that increased use of IPM techniques could reduce ETU residues on food crops (as well as applicator exposure both on food crops and nonfood products). While IPM strategies show promise for reducing insecticide use on many crops, the overall prospect for comparable fungicide reduction is less promising because: 1) current IPM practices for plant disease control typically include fungicides as an integral part of the overall strategy; 2) although cultural practices

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and biological control can bring about disease reduction, they are rarely entirely effective by themselves and are often used as supplements to chemical control; and 3) while monitoring and forecasting techniques have successfully brought about reductions in frequency of fungicide use, some fungicide applications are still necessary for effective disease control.

Genetic resistance remains one of the primary alternatives to fungicide use, but is limited on certain crops due to the lack of suitable host resistance or other factors. While the IPM approach will continue to bring about reductions in total fungicide use, it is unlikely that fungicides will be entirely replaced on most crops.

4. Reassess Tolerances for EBDC Residues; Establish Tolerances for ETU Residues

The Agency's risk assessment of the EBDC fungicides focused primarily on dietary exposure to ETU as a result of various food and feed uses of the EBDC's. Although ETU is recognized as a contaminant in EBDC formulations and as a conversion product of the EBDC's, no tolerances for ETU have been established. (For enforcement purposes, ETU is considered to be covered by the EBDC tolerances. It is assumed that ETU may be present at levels equivalent to a stoichiometric conversion of EBDC, i.e., 100 percent conversion on a mole-per-mole basis.) Likewise, no meat, milk, or egg tolerances have been established for the EBDC's, although the EBDC fungicides are used on numerous commodities that are used as animal feed.

For purposes of calculating worst-case dietary risk, the Agency assumed--given the absence of ETU tolerances--that 100 percent of EBDC residues convert to ETU and that EBDC residues are present at current tolerance levels. Worst-case dietary exposure could, in all likelihood, be reduced if EBDC tolerances were reassessed and lowered and if ETU tolerances were established. Moreover, establishing tolerances for ETU to replace the single recommendation for the EBDC's would be consistent with the joint recommendation of the World Health Organization and the Food and Agricultural Organization of the United Nations (WHO 1970).

However, the data base to support EBDC tolerances is not complete. The relative dearth of residue data, casts doubt on existing tolerances. The Agency intends to pursue the question of tolerances for EBDC residues in the registration standard review planned for the near future. At that time, dietary residue and other exposure data, as well as necessary chronic and other toxicology studies, will be required. However, until the necessary tolerance/dietary exposure data become available, the Agency cannot proceed either to reassess EBDC tolerances or to establish tolerances for ETU.

B. Measures to Reduce Exposure to Mixer-Loaders/ Applicators

1. Classify the EBDC's for Restricted Use and Require Applicator Certification

Under FIFRA, hazardous pesticides may be classified for restricted use and limited to use only by certified applicators. This measure would remove the EBDC fungicides from the open market and restrict their use to certified applicators and persons under their direct supervision. Classified for restricted use, the EBDC's would be available only to those users who have undergone a certification program. Such programs, administered primarily by the states, employ various methods to determine that applicators are certifiable as competent to use restricted use pesticides. Certification programs are designed to encourage greater responsibility on the part of applicators and thereby reduce exposure and adverse effects.

All applicators, both professional and non-professional, would be required to obtain certification. This requirement would directly affect primarily home garden applicators. Information available to the Agency indicates that 0.5 to 1.0 million pounds of EBDC's (active ingredient) are sold for home garden use yearly. About 90 percent of this poundage is sold as one-pound packages of 40-percent wettable powders, the remaining 10 percent as 5-percent dust in one-pound packages (Pelletier 1979a).

2. Protective Clothing (Long-Sleeved Shirts and Long Pants of Closely Woven Fabric, and Impermeable Gloves)

Dermal exposure to the EBDC's can occur during mixing, loading, and maintenance of application equipment and during ground spray and aerial applications.

Protective clothing, comprised of long-sleeved shirts and long pants of closely woven fabric and impermeable gloves, is expected to reduce risk by 75 to 80 percent (Mittleman 1979). If implemented, protective clothing requirements would have a minimal impact on economic benefits.

Concern has frequently been expressed over whether protective clothing is actually worn in very warm climates such as Florida, where EBDC's are heavily used. This concern is generally well founded but probably does not apply to EBDC since most EBDC use in the south takes place during the cooler winter and spring months.

3. Packaging or Formulation Changes

Packaging and formulation changes could reduce exposure to applicators during mixing and loading of EBDC's. These changes are intended to reduce the quantities of dust created by handling of wettable powders, the most common formulation.

a. Package Wettable Powders in Water-Soluble Materials

When water-soluble bags containing wettable powders are immersed in water, the bag dissolves and its contents are released and mixed. No dust is generated during either pouring or mixing. The packaging of wettable powder formulations in water-soluble bags would reduce by at least 95 percent applicator exposure to dusts that would otherwise be released during pouring and mixing (Severn 1979).

b. Eliminate Wettable Powders in Favor of Wet Flowable Formulations

Wet flowable formulations are emulsions of the EBDC's in water that are poured directly in the spray tanks for application. No dust is generated during pouring or mixing the product. To substitute wet flowable formulations for wettable powder formulations of the EBDC's would eliminate exposure to dust during mixing and afford the applicators the same degree of protection as would repackaging in water-soluble bags (i.e., a 95-percent reduction in exposure and risk). A wet flowable formulation of mancozeb is registered.

c. Eliminate Wettable Powders in Favor of Dry Flowable Formulations

Dry flowable formulations consist of particles larger than those found in wettable powders. These formulations generate less dust than the wettable powders but more than wet flowable formulations or wettable powders packaged in water-soluable bags.

Adoption of any of these three alternative changes in formulation or packaging would increase the cost of EBDC's by $0.75 per pound, or approximately $19 million per year for all EBDC usage. Registrants would have the option of selecting and implementing the alternative(s) of their choice.

V. REGULATORY DECISION

FIFRA requires the Agency to consider the risks and benefits of a pesticide in deciding whether it should be registered. Accordingly, this section describes the key risk issues, summarizes the salient benefits of EBDC's, states the risk/benefit conclusions and reaches a regulatory decision.

A. Summary of Risks

1. RPAR Risk Criteria and Rebuttals

As detailed in Section II, the Agency has determined that the three risk criteria cited in the RPAR notice and in PD 1 as bases for the presumption against the EBDC's have not been rebutted. These criteria are: (1) acute hazards to aquatic species of wildlife (mancozeb), (2) oncogenicity (EBDC's and ETU) and (3) teratogenicity (ETU).

Two of these original risk criteria--oncogenicity and teratogenicity--represent potential risks to humans. Animal studies show that maneb, zineb and ETU are oncogenic in rats and mice. Likewise, several studies show that ETU is teratogenic in rats. The third criterion--acute hazards to aquatic wildlife--is no longer a concern for cranberry fields but is a concern for the use of mancozeb on commercially grown wild rice.

The PD 1 also cited three areas of potential concern--thyroid toxicity, mutagenicity and skin sensitization.

The Agency has determined that the thyroid effects of the EBDC's exceeded the risk criterion for a rebuttable presumption. This criterion was not rebutted.

Available test data for EBDC's are inconclusive and thus do not meet the mutagenicity risk criterion of "multitest evidence." The data for ETU meet the RPAR criterion of multitest evidence for microbial systems only. However, the data for both the EBDC's and ETU are incomplete and additional testing is needed before the Agency can judge the potential mutagenicity, if any, of these chemicals to humans. The Agency's conclusions regarding potential mutagenic risk are presented in V.A.3.d. below.

The Agency has reviewed the data submitted on skin sensitization and has concluded that the RPAR risk criterion was not met.

Rebuttal arguments and the Agency's responses regarding risk assessment are discussed in V.A.3. below.

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2. Exposure Assessment

The avenues of exposure to ETU as a result of the various fungicidal uses of the EBDC's are dietary (oral), dermal and inhalational. An estimated 60,000 pesticide applicators, both professional and nonprofessional, work with the EBDC's. Dietary exposure potentially affects the entire United States population.

Human exposure to EBDC's was calculated for the United States population based on estimated consumption of dietary residues of ETU in treated crops. With limited ETU data, assumptions were made about the conversion of EBDC's to ETU and other factors. Upper limit (worst case) and lower limit (lowest case) estimates of exposure were estimated to be 0.00365 mg/kg/day and 0.00024 mg/kg/day of ETU, respectively. Although several rebuttals criticized the Agency for over-estimating the upper limit of exposure, it is possible that the Agency underestimated the upper limit, since available data on possible residues of ETU in drinking water, meat, milk, eggs, animal feed and processed foods were not available. Uncertainty has also been added to the dietary exposure estimates because of limited data on: (1) ETU residue data on most raw agricultural commmodities, (2) data on conversion of EBDC to ETU during food processing and (3) animal metabolism data. Data in these areas are needed to accurately estimate dietary exposure.

In the near future the reregistration review of the EBDC's will identify the residue chemistry data gaps and require the data to be generated. When these data are available the Agency will be able to more accurately estimate exposure for risk assessment purposes, to assess the adequacy of tolerances and to reduce the uncertainty associated with the current dietary exposure estimates.

Applicator exposures were estimated for ETU inhaled or absorbed dermally during mixing or loading and during ground spray or aerial applications. Field data were used along with reasonable assumptions to estimate daily, seasonal and annual exposures. On the one hand, the fact that the available studies were not complete and that the limited dermal penetration data for EBDC's and ETU add uncertainty to the exposure estimates. On the other hand, the Agency has recently received preliminary data showing that ETU has been found in the urine of applicators. Dermal absorption studies in rats are needed for each of the EBDC's to assure the accuracy of the applicator exposure estimates. Other studies may be identified in the near future in a reregistration review of the EBDC's.

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3. Risk Assessment

After estimating exposure, the Agency evaluated the potential risks of the EBDC's for each unrebutted risk criterion.

a. Acute Toxicity to Aquatic Organisms

Since mancozeb is used only on commercially grown wild rice and since current cultivating practices prevent most non-target organism exposure, it was concluded that the risks of acute toxicity to aquatic organisms are not unreasonable as long as an appropriate warning is added to the label (see V.D. for label wording).

b. Oncogenicity

The oncogenic potential for the EBDC's and ETU has been evaluated qualitatively and quantitatively.

Qualitatively, the Agency has concluded that the EBDC's may have the potential to cause oncogenic effects in humans based on the animal data. However, the Agency has recognized several arguments which attach uncertainty to quantitative assessment of risk.

First, the Agency agrees with rebuttors that there are several deficiencies in the EBDC studies which make them unreliable for use in a risk assessment. Consequently, these studies were not used for the quantitative risk assessment.

Second, it was suggested by the rebuttors that both the liver and thyroid tumors observed in animals were induced indirectly. The Agency recognized that this is possible, but has concluded that additional testing is needed to support this hypothesis. Such testing includes long term animal feeding, metabolism and additional mutagenicity tests. In addition, the need for chronic feeding studies will be assessed during the reregistration review. Until the mechanism of action is clarified, a risk assessment model which assumes that EBDC and ETU are tumor initiators (i.e., a linear low dose model) will be used.

Third, the rebuttors cited several "negative" animal and epidemiological studies as evidence that the EBDC's and ETU are not oncogenic. The Agency acknowledged that such studies appeared to show negative results. But the Agency found shortcomings in these studies and concluded that they did not prove that the EBDC'S and ETU are not potentially oncogenic.

Using a linear low dose (one-hit) model and assuming that this provides an upper bound of risk, the Agency quantitatively assessed the potential lifetime oncogenic risks of the general public and applicators exposed to EBDC'S and ETU.

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The Innes et al. (1969) mouse liver tumor data for ETU were used, since they were the most sensitive results available. Based on the estimated exposures, the lifetime risks to the United States population from estimated dietary residues of ETU ranged from 5×10^{-4} (upper limit exposure) to 5×10^{-5} (lower limit exposure). Risks to applicators over a 40-year working period ranged from 1×10^{-2} to 9×10^{-5}, depending on the crop method of application and phase of operation (mixing/loading versus application).

In summary, the Agency assumed that the EBDC's and ETU may pose a potential oncogenic risk to man based on evaluation of animal data. In the absence of adequate oncogenicity and mutagenicity information to resolve the mechanism of action and the choice of a risk assessment model, the Agency estimated risks based on the one-hit model. The Agency views these estimates as only rough indications of an upper bound of potential effects. Moreover, the uncertainties associated with the exposure data indicate that the risk estimates may be higher or lower than the actual risks. The Agency has taken these issues into account in reaching its regulatory decision.

c. Teratogenicity and Thyroid Toxicity

Teratogenic and thyroid toxicity risks were evaluated by comparing the NOEL in animal studies with estimated human exposure levels to determine whether the margins of safety (MOS) were adequate. The MOS's for the United States population ranged from 200 to >1,000 for teratogenicity and from 70 to >1,000 for thyroid toxicity. Some of these MOS's are not acceptable. However, the exposure estimates upon which these MOS's were based were extremely crude due to the lack of actual food residue data for ETU and the EBDC's and due to the lack of mammalian metabolism studies for conversion of EBDC's to ETU. Consequently, additional metabolism studies are being required at this time. Further residue data will be required during a reregistration review in the near future. These data will be used to verify the exposure estimates upon which the MOS's are based. The MOS's for applicators (<10 to 1,000) are not acceptable and protective clothing must be added to the label in order to prevent unreasonable adverse effects.

d. Mutagenicity

Based upon review of both published and unpublished studies to date, including the large data bases provided by Agency-sponsored and international collaborative testing programs, the Agency has determined that the EBDC fungicides have been inadequately tested for mutagenicity and therefore the data are inconclusive. Additional testing is needed on each of the six EBDC chemicals before the Agency can adequately judge their potential mutagenicity.

A review of the data base on ETU has led to the conclusion that this chemical meets the criterion for mutagenicity on the basis of multitest evidence in microbial systems, and no further testing for specific genetic end-points (gene mutation, chromosome aberrations, DNA damage/repair) is needed. However, the positive results reported in some short-term mammalian assays (specifically, mammalian cell transformation in vitro), which are of significant relevance to the potential oncogenicity of ETU and the EBDC's prompts the need for confirmation in other short-term assays of this type for both ETU and each of the six EBDC's.

e. Alternative Fungicides

One risk issue referred to in the Benefits Chapter is that information on the risks of the alternative fungicides to the EBDC's is incomplete. Without such information the Agency cannot clearly determine whether the risks of the alternatives are lower or higher than those of the EBDC's. These data will be obtained for most alternatives in the near future under the Agency's data call-in and reregistration review programs. Meanwhile, however, the lack of risk data on the alternative fungicides adds uncertainty to judgment about the risks of EBDC's.

B. Summary of Benefits

Section III of this document detailed the benefits of the EBDC's. Briefly, the EBDC's are the most used fungicides in the United States, accounting for about one third of the organic fungicides applied to agricultural crops. The EBDC's also have important industrial uses such as in water cooling systems, sugar mills and pulp and paper mills. These chemicals are effective against a broad spectrum of fungi and plant diseases caused by fungi. They mix well with other pesticides and usually are less expensive than alternative fungicides.

The benefits of the EBDC fungicides were jointly assessed by the U.S. Department of Agriculture and the EPA in terms of the economic impacts which would result if the uses under review were cancelled and users were forced to employ available alternatives. Major economic impacts are expected should the EBDC fungicides be cancelled for lettuce, wild rice and grass seed. Moderate impacts are anticipated from cancellation of bananas, mushrooms, spinach, sweet corn, green peppers, Christmas trees/pine nurseries and flower/foliage plants. Minor impacts are projected for producers of apples, grapes, lima beans, tobacco and small grains, although certain individual growers could experience major impacts. Minor impacts are projected for all other uses of the EBDC's. However, these aggregated conclusions only give part of the benefits picture.

First, the projected economic impacts of EBDC cancellation were calculated assuming the continued availability of alternative fungicides. If the registrations of one or more of these alternatives were cancelled, the economic impacts of EBDC cancellation could increase significantly. When fungicides are reviewed one-by-one, the benefits of any single fungicide or group of fungicides can be distorted so that the actual economic impact of cancellation is not accurately conveyed. This is demonstrated by the fact that the Preliminary Benefit Analysis for EBDC's indicates total impacts to be approximately $150 million or one to two percent of the total economic benefit of fungicides--a seemingly minor contribution considering EBDC's account for 35 percent of organic fungicide use. Benefits for the remaining chemicals will increase disproportionately after a fungicide is cancelled.

Second, grower impacts would vary by region, although all regions would be affected. In general, individuals in the eastern coastal areas would be hardest hit, with the Southeast suffering the greatest losses, since the climatic conditions there tend to intensify the incidence of diseases which are most destructive to fruits and vegetables. The West would suffer fewer losses in production than the East, but heavy reliance on protective postharvest treatments of fruits and vegetables to protect them from spoilage during shipping and marketing would mean the impacts would still be significant. While absolute losses would be large for the Midwest, relative losses would tend to be lower because while all the seeds for their field crops are treated with fungicides, the vast acreages cultivated would moderate the percentage of crop value lost. Because Florida's warm, humid climate is more conducive to the types of fungal growth controlled by EBDC's, Florida growers would be more severely impacted by cancellation of EBDC's than would growers in other states. California, Arizona and Ohio growers would also suffer a disproportionate share of losses.

Third, should the EBDC fungicides be cancelled, consumer price increases would be expected for lettuce, spinach, bananas, green peppers, snap beans, watermelon and mushrooms. No consumer impacts are expected from all other uses of the EBDC's.

Fourth, the loss of the most efficacious fungicides could also result in incidents of human poisoning due to the presence of mycotoxins in produce infected with fungi. To date, mycotoxins of human consequence have been reported to occur in four important food crops--peanuts, wheat, potatoes and apples. The potential for mycotoxin problems in other crops is unknown.

The Agency has concluded that the EBDC's have significant benefits to agriculture, industrial users and consumers.

C. Risk-Benefit Conclusions

Section IV presented three regulatory options - (1) continue registrations as is, (2) continue registrations with additional requirements and (3) cancel registrations.

In light of the estimated risks and benefits the Agency has concluded that neither Options 1 or 3 are appropriate. Option 1 is rejected because there are several risk areas which meet the Agency's risk criteria and require regulatory action. Option 3 is inappropriate because risk in certain areas (acute toxicity to aquatic organisms and risks of teratogenicity and thyroid effects to applicators) may be reduced adequately through label changes and because the other risk areas (oncogenic, mutagenic, teratogenic and thyroid effects to the general population) have too many uncertainties associated with them to determine if cancellation is appropriate.

Option 2 has been selected for the following reasons:

1. The potential risk of acute toxicity to aquatic organisms resulting from EBDC use on commercial rice may be reduced satisfactorily by adding a statement to the label which warns users of the product's toxicity to fish and of potential environmental hazard (see Section V.D. for exact label wording).

2. Risks of teratogenicity and thyroid toxicity to commercial and agricultural applicators can be adequately reduced by requiring that protective clothing be worn. Such clothing includes long pants, long sleeved shirt, impermeable gloves, hat and boots. These must be specified on the label.

3. The issues of whether EBDC's or ETU pose a potential risk of oncogenicity, mutagenicity, teratogenicity and thyroid effects to man are subject to many uncertainties. The laboratory data on oncogenicity and mutagenicity are not adequate to resolve key scientific issues such as the mechanism of action of EBDC's and ETU. The data for determining dietary and applicator exposure are also not adequate to assess risks. Although oncogenic risks were estimated for ETU, the uncertainties surrounding the risk numbers make them difficult to use for regulatory decisions. Finally, risk data for the alternative fungicides are incomplete so that they cannot be compared to the EBDC's or ETU.

Additional data on the EBDC's, ETU and alternative fungicides are required to enable the Agency to perform a proper risk assessment (see Section V.D. for list of required tests). Although not all data that are needed can be identified at this time, the reregistration review for EBDC's and other fungicides scheduled for the near future will ascertain in greater detail what additional data are required to support the continued registration of these products.

Meanwhile, a risk reduction measure which will reduce human dietary exposure is to highlight preharvest intervals on non-commercial labels so that home garden users will be encouraged to comply with them.

During the time period required for registrants to generate the requested data and for the Agency to evaluate them, it is anticipated that unreasonable adverse effects will not occur as long as registrants comply with the label changes and data requirements listed in V.D. below.

D. Regulatory Actions

Based on the above conclusions, the Agency has determined that the RPAR will be ended; the registrations of EBDC's will be continued as long as registrants comply with the following terms and conditions:

1. Add a wildlife warning for use of mancozeb on commercially grown wild rice:

   "This product is toxic to fish. Discharge from treated areas may be hazardous to fish in neighboring areas. Do not contaminate water by cleaning of equipment or disposal of wastes."

2. Add a statement to the label requiring protective clothing (long pants, long sleeve-shirt, impermeable gloves, hat and boots) be worn during mixing and loading.

3. Highlight preharvest intervals on labels of non-commercial (homeowner) products.

4. Submit the following studies within 18 months of receipt of a letter issued from the Agency in accordance with Section (3)(c)(2)(B) of FIFRA:

   a. Metabolism studies designed to demonstrate the in vivo conversion of the various

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EBDC's to ETU and other metabolites. Unless adequate justification is given, these studies must be performed on each of the six currently registered EBDC active ingredients. A metabolism study on ETU will not be required at this time because the Agency believes a recent study by the National Toxicology Program (1982) may provide adequate information.

b. Dermal absorption studies designed to demonstrate the dermal penetration of each of the EBDC's and ETU. Unless adequate justification is given, these studies should be performed on each of the six currently registered EBDC's. The study requires application of various doses of radiolabeled test compound to the shaved skin of male rats, followed at specific intervals after dosing, by total urine collections, determination of blood concentration, determination of the quantity in the body and determination of the quantity remaining on the skin.

c. The following mutagenicity studies on each of the six registered EBDC's:

(1) Ames Assays for gene mutation in Salmonella typhimurium (TA strains), or Escherichia coli WP2, performed with/without the use of mammalian metabolic activation (S-9) from induced (Aroclor 1254 liver microsomes from both mouse and rat strains found to respond positively in oncogenicity testing.

(2) Host-Mediated Assays in the same strains of mice and rats, by both oral and parenteral routes of administration, as in (1), with appropriate microbial or mammalian indicator cells. using the same bacterial indicators as in (1)

(3) In vitro Mammalian Cell gene mutation assays, using the mouse lyphoma cell line L5178Y (for TK), or Chinese Hamster Ovary Cells (CHO, for HGPRT), performed with/without the use of mammalian metabolic activation systems (S-9) derived from Aroclor 1254 induced liver microsomes from mice and rats.

(4) In vitro Cytogenetic Assays, for both gross chromosome aberrations (clastogenesis), and for sister-chromatid exchanges (SCE's), in replicate cultures of rodent, hamster or human cell lines or strains, or human lymphocytes, performed with/without the use of metabolic activation (S-9) from induced mice and rats.

(5) Primary Hepatocyte Repair Test for unscheduled DNA synthesis (UDS), performed with the same strains of rats and mice as in (1), employing both in vivo as well as in vitro exposure to test compounds.

d. Mammalian Cell Transoformation Assays on each of the six EBDC's and ETU, with or without metabolic activation (as appropriate) in one of the following cell systems capable of detecting initiation-- Syrian hamster embryo (SHE, clonal or focus assay), or mouse embryo fibroblasts from the strains Bagg albino (BALB/3T3), or C3H (CeH-10T1/2) -- and in one of the following viral cell cutures capable of detecting enhancement of transformation by chemicals (promotion) -- SHE cells infected with simian adenovirus (SA7/SHE), or Fischer rat embryo cells infected with Rauscher leukemia virus (RLV/RE), or mouse embryo cells infected with AKR (mouse) leukemia virus (AKR/ME).

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